2012-08-28

Obstructive sleep apnea treatment with continuous positive airway pressure therapy improves renin angiotensin system activity

Nicholl, David

UNIVERSITY OF CALGARY

Obstructive Sleep Apnea Treatment with Continuous Positive Airway Pressure Therapy Improves Renin Angiotensin System Activity

by

David Nicholl

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCE

DEPARTMENT OF MEDICAL SCIENCES

CALGARY, ALBERTA

AUGUST, 2012

ABSTRACT

Background Obstructive sleep apnea (OSA) is strongly associated with cardiorenal disease. Limited studies suggest that renin angiotensin system (RAS) activation may mediate this relationship. We sought to determine the effect of continuous positive airway pressure (CPAP) on the hemodynamic and circulating RAS component responses to Angiotensin II (AngII) infusion.

Methods Twelve moderate-severe OSA subjects with hypoxia were studied in high-salt balance before and 1 month after starting treatment with CPAP. Mean arterial pressure (MAP), plasma renin activity (PRA), and aldosterone were measured in response to AngII (3ng/kg/minx30min, 6ng/kg/minx30min, 30min recovery).

Results CPAP corrected OSA; reduced MAP (95±2 vs 89±2mmHg, p=0.019), aldosterone (179±27 vs 115±14pmol/L, p=0.006), and protein excretion (69[39,341] vs 48[22,204]mg/day, p=0.002); and increased MAP sensitivity to 3ng/kg/min AngII (10±2 vs 15±2mmHg, p=0.019), but not 6ng/kg/min AngII or recovery. RAS component sensitivity was unaffected.

Conclusions CPAP treatment decreased RAS activity and increased hemodynamic sensitivity to AngII, supporting a role for the RAS in mediating OSA-induced hypertension.

ACKNOWLEDGEMENTS

I am grateful to Dr. Sofia Ahmed, Dr. Pat Hanly, Dr. Marc Poulin, Dr. Brenda Hemmelgarn, and Dr. Turin Chowdhury for their guidance, supervision, and mentorship over the last few years; Ms. Darlene Sola for her amazing work running our study days; Mr. George Handley for his unparalleled management of CPAP in our study participants; Ms. Brenda Green and Ms. Patty Nielsen for their clerical assistance; the members of our laboratory, Ms. Michelle Mann, Dr. Magdalena Sarna, Dr. Ahmed Abdi Ali, and Ms. Ann Zalucky; Dr. Matthew James for agreeing to be my external examiner; the FMC Sleep Centre and Healthy Heart Sleep Company for subject recruitment; the Canadian Institute of Health Research, Alberta Innovates - Health Solutions, the Cosmopolitan International Club of Calgary, the Division of Nephology, and the FMC Sleep Centre Development Fund for funding this research; and of course, the participants themselves, without whom none of this would have been possible.

DEDICATION

This thesis is for my family, friends, colleagues, and mentors for all of their guidance and support over the last 2 years.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACE, angiotensin-converting enzyme
AHI, apnea hypopnea index
AngI, angiotensin I
AngII, angiotensin II
ARB, angiotensin II type-1 receptor blocker
AT_1, angiotensin II type-1
AT_2, angiotensin II type-2
BMI, body mass index
BP, blood pressure
CAPD, continuous ambulatory peritoneal dialysis
CHD, conventional hemodialysis
CIH, chronic intermittent hypoxia
CKD, chronic kidney disease
CPAP, continuous positive airway pressure
CSR, Cheyne-Stokes respiration
DBP, diastolic blood pressure
eGFR, estimated glomerular filtration rate
eNOS, endothelial nitric oxide synthase
ESRD, end-stage renal disease
FF, filtration fraction
FMC, Foothills Medical Centre
MAP, mean arterial pressure
MetS, metabolic syndrome
NHD, nocturnal hemodialysis
NO, nitric oxide
NPD, nocturnal peritoneal dialysis
NS, non-significant
OSA, obstructive sleep apnea
OSAS, obstructive sleep apnea syndrome
PP, pulse pressure
PRA, plasma renin activity
RAS, renin angiotensin system
RDI, respiratory disturbance index
RIA, radioimmunoassay
SaO_2, oxyhemoglobin saturation
SBP, systolic blood pressure
SE, standard error
UTPE, urinary total protein excretion

EPIGRAPH

If you don't go after what you want, you'll never have it. If you don't ask, the answer is always no. If you don't step forward, you're always in the same place.

-Nora Roberts

CHAPTER ONE: INTRODUCTION

Overview

Chronic kidney disease (CKD) is a growing public health problem worldwide.[1-3] Despite advances in prevention and treatment, the incidence and prevalence of CKD are increasing,[1, 2] and the burden of disease remains high.[4-8] Consequently, novel therapies for the treatment and prevention of kidney function loss are greatly needed. There is growing recognition of the widespread incidence and health consequences of obstructive sleep apnea (OSA).[9-18] While there is a well-accepted relationship between OSA and the development of hypertension,[9, 12, 19-25] there is also increasing evidence suggesting an association between sleep-disordered breathing and the presence of kidney disease in the form of proteinuria,[26-34] although not all studies have confirmed this relationship.[35-37] We and others have shown an increased prevalence of OSA in CKD[38-44] and end-stage renal disease (ESRD).[38, 42, 43, 45-51] Further, there is a clear association between nocturnal hypoxia and loss of kidney function.[52] We have also reported an increased prevalence of nocturnal hypoxia in patients with CKD and ESRD.[43] Of importance, the mechanism underlying the loss of kidney function associated with OSA is unclear, but limited studies suggest a prominent role of the renin angiotensin system (RAS), activation of which results in a predisposition to kidney disease.[53]

Obstructive Sleep Apnea

Definition

Obstructive sleep apnea (OSA) is a chronic medical disorder characterized by a complete or partial cessation of breathing during sleep, caused by pharyngeal occlusion, which is associated with intermittent hypoxia and sleep disruption.[54, 55] OSA is considered present when these breathing disturbances occur with a minimum frequency of 5 events per hour of sleep and

last for at least 10 seconds.[54, 55] These events occur due to anatomical and physiological features of the upper airway and their neural control or as a result of craniofacial parameters.[56] OSA was first properly documented and described in the 1960s,[57] though there is evidence that sleep apnea has been recognized throughout human history, with reports dating from as far back as the 4th century BC and throughout the 19th and 20th centuries AD.[58]

Diagnosis

OSA is diagnosed by an overnight sleep study (polysomnography or portable monitoring) which monitors breathing during sleep and expresses the frequency of respiratory disturbances as either the apnea hypopnea index (AHI) or the respiratory disturbance index (RDI).[59] The AHI and RDI are comparable indices for determining the number of respiratory events.[60, 61] Polysomnography is the gold standard for diagnosing OSA.[55] However, portable monitoring is an acceptable alternative in patients suspected of having OSA.[62-64] Mild, moderate, and severe OSA are defined as an AHI or RDI $\geq$5 hr^{-1}, $\geq$15 hr^{-1}, and $\geq$30 hr^{-1}, respectively.[54] Obstructive sleep apnea syndrome (OSAS) describes the combined features of an RDI $\geq$5 and at least one of the symptoms attributed to sleep apnea known to respond to treatment, such as excessive daytime sleepiness, loud snoring, observed apneas, nocturnal choking, and sleep disruption.[54, 55, 59, 65] Nocturnal hypoxia, which is often caused by and associated with OSA, is defined as an oxyhemoglobin saturation (SaO_2) <90% for $\geq$12% of night.[12]

Epidemiology

In the general population, mild OSA (RDI $\geq$5) occurs in 24% of men and 9% of women, while moderate OSA (RDI $\geq$15) occurs in 9% of men and 4% of women.[66] However, more recent studies have reported the prevalence of asymptomatic OSA to be as high as 20-30% in the middle-aged population.[67, 68] The variance in prevalence estimates for OSA can be explained by

the populations studied and the inclusion/exclusion of daytime symptoms for a diagnosis of OSA. For instance, the prevalence of mild OSAS (RDI ≥5 and daytime symptoms) has been reported to occur in 4% of men and 2% of women.[66] The same study reported the prevalence of mild asymptomatic OSA (RDI ≥5) to occur in 24% of men and 9% of women.[66] Prevalence estimates also vary with age and gender.[66, 69-71] Importantly, an estimated 82% of men and 93% of women with moderate to severe sleep apnea syndrome are not clinically diganosed.[67]

Complications and Risk Factors

OSA causes excessive daytime sleepiness, inattention, fatigue, and impairment of sleep quality,[55, 72] which in turn impairs daytime and neurocognitive function,[73-76] induces or exacerbates cognitive deficits,[73, 74] diminishes quality of life,[77] and increases the likelihood of errors[73, 74] and both motor vehicle[78-85] and occupational[86, 87] accidents. OSA increases the risk of systemic hypertension,[9, 12, 23-25] mild pulmonary hypertension,[88-92] stroke,[14, 93-96] cardiovascular disease,[13, 18, 97-102] including arrhythmias,[99, 103, 104] atherosclerosis,[18] myocardial infarction,[97, 100] and heart failure,[98, 101] and both cardiovascular[105-107] and all-cause mortality.[105, 107-111] OSA may also increase the risk of type 2 diabetes,[15, 112, 113] dyslipidemia,[17] metabolic syndrome [10, 16, 114, 115] (MetS; defined as a constellation of abdominal obesity, hypertension, dyslipidemia, and dysglycemia[116]), and perioperative complications (due to intubation difficulty and impaired arousals from sedatives).[117] Idiopathic fibrosis[118] and cancer[11] have been associated with OSA. Further, OSA may accelerate the deterioration of kidney function.[52, 119-123]

Definite risk factors for OSA include obesity, male gender, aging, menopause, vascular disease, and craniofacial and upper airway soft tissue abnormalities (abnormal maxillary or short mandibular size, tonsillar hypertrophy, adenoid hypertrophy, and a wide craniofacial base).[56, 66, 68, 124, 125] Potential risk factors for OSA include heredity, race and ethnicity, current smoking (but

not past smoking), and nasal congestion.[56, 66, 68-71, 124, 126, 127] Diabetes may also be a risk factor for sleep-disordered breathing.[45, 128] OSA is also more prevalent in African Americans compared to Caucasians of a similar body weight[129] and the prevalence of OSA in Asia is similar to that of North America despite a lower body weight.[130, 131] Racial differences may be related to differences in craniofacial structure.[130, 131]

Younger people with OSA are more likely to have hypertension,[132] atrial fibrilliation,[103] and suffer greater all-cause mortality.[108, 109] Overall, OSA patients use more medical resources and have a greater medical burden than individuals without OSA.[14, 96, 102, 111, 124, 133] The signs, symptoms, and consequences of OSA are a direct result of the alterations that occur due to the repetitive collapse of the upper airway and include hypoxemia, hypercapnia, sleep fragmentation, swings in intrathoracic pressure, and increased sympathetic nervous system activity, during sleep over the period of months to years.[55, 127, 134]

Treatment

Treatment of OSA involves behaviour modification (including weight loss, exercise, sleep posture and hygiene, alcohol avoidance, and avoidance of certain medications) and OSA-specific therapies including positive airway pressure, oral appliance, and surgery.[59, 127] Continuous positive airway pressure (CPAP) is considered the first line therapy.[55, 135] The positive airflow pressure that is generated by the airflow turbine pump splints open the pharynx, thereby preventing apneas, hypopneas, snoring, and sleep fragmentation.[136] Indeed, CPAP therapy effectively reduces respiratory events and hypoxia during sleep,[135, 137-139] daytime sleepiness,[75, 139-143] blood pressure,[114, 139, 140, 144-156] hospitalizations,[157] MetS,[114] cardiovascular events,[13, 106, 158] motor vehicle accidents, [79, 80] and mortality[106, 107, 159, 160]; improves quality of life,[75, 139] cognition,[75, 161] driver performance,[84] and indices of glycemic control[112, 114]; and has

been demonstrated to be cost-effective.[80, 162-166] CPAP therapy has also been demonstrated to reduce oxidative stress,[167-169] pro-inflammatory cytokines,[168, 170-173] endothelin-1,[174] and sympathetic nervous system activity,[172, 173, 175-177] while concomitantly improving baroreflex sensitivity (an index of cardiac sympatho-vagal balance)[178] and endothelial function.[179, 180] Importantly, discontinuing therapy for even 1 night may mitigate the benefits of CPAP.[139, 181-183]

Chronic Kidney Disease

Definition, Epidemiology, Risk Factors, and Complications

Chronic kidney disease is defined as either reduced kidney function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2)[184] for 3 or more months or evidence of kidney damage on urinalysis, imaging, or biopsy.[1] CKD is a health burden affecting over 2 million Canadians.[3] At present, the prevalence of CKD in the United States has been estimated to be 13.1%.[2] However, the incidence and prevalence of kidney disease are rising, outcomes are poor, and costs to the health care system are high.[1, 2, 185] The major adverse outcomes of CKD, regardless of cause, include progression to ESRD, complications of decreased kidney function, and cardiovascular disease.[1, 4, 5, 7, 8, 186-189] Co-morbid diabetes, hypertension, and proteinuria may further promote the development of cardiovascular disease in CKD patients.[190] In patients with cardiovascular disease, diabetes, or hypertension, the presence of CKD acts as a risk multiplier, especially if proteinuria is present.[191] Proteinuria, even within the normal range, is a powerful predictor and potential contributor to cardiovascular events,[192-204] CKD progression,[198, 199] ESRD,[198, 199, 205, 206] and all-cause mortality.[193, 195, 197-199, 202, 207] As a result of the high cardiovascular mortality, which occurs well before progression to ESRD,[186, 188] only a minority of CKD patients survive long enough to require renal replacement therapy (defined as dialysis or renal transplantation).[188] Aging,[185, 208-210] male gender,[185, 211] obesity,[185, 212, 213] smoking,[214-219]

diabetes,[190] MetS,[220-222] dyslipidemia,[223, 224] and hypertension[225, 226] are all risk factors for CKD. Patients with CKD are at high risk for progression to dialysis and cardiovascular disease,[4, 5, 186, 227, 228] and despite recent advances in detection and treatment, including hypertension control, anemia management, and dialysis adequacy, progression of disease and mortality remain high.[4-8] Consequently, CKD remains a significant burden to the health care system and novel therapies are needed for the prevention and treatment of loss of kidney function. An improved understanding of non-traditional risk factors that are present at early phases in CKD may lead to novel therapeutic strategies for preventing loss of kidney function.

Obstructive Sleep Apnea and Chronic Kidney Disease

Epidemiology

We and others have shown an increased prevalence of OSA (RDI ≥15) ranging from 27-54% in CKD patients[39-43] and 45-70% in patients with ESRD[38, 42, 43, 45-50]. Further, almost 50% of CKD and ESRD patients have significant nocturnal hypoxia (SaO_2<90% for ≥12% of night).[43] Conversely, CKD is more prevalent in OSA patients,[229-231] with a reported prevalence of 18% in normotensive, non-diabetic patients with severe OSA (RDI ≥30).[231] Nocturnal hypoxia has also been associated with accelerated loss of kidney function.[52] Further, while hypertension occurs frequently in patients with sleep apnea,[9, 12, 23-25] the combination of elevated blood pressure and sleep apnea is even more common among CKD patients,[232] suggesting a potential interaction or additive effect. Severe OSA has been associated with increased serum Cystatin C (a biomarker considered to reflect latent renal dysfunction and cardiovascular risk) levels,[122, 123] while increasing OSA severity has been associated with reduced renal function.[121, 123] OSA and nocturnal hypoxia have also been demonstrated to be independent risk factors for cardiovascular and all-cause mortality in dialysis patients.[233-235] Aging,[56, 66, 124, 185, 208, 209] male gender,[56, 66, 124,

[185, 211] obesity,[56, 66, 124, 212, 213] and smoking[124, 126, 214-219] are risk factors shared by CKD and OSA. Further, consequences of OSA, including type 2 diabetes,[190] MetS,[220-222] dyslipidemia,[223, 224] and hypertension[225, 226] are also risk factors for CKD. Consequently, the relationship between OSA and nocturnal hypoxia with kidney disease is most likely bi-directional, with the presence of one exacerbating the other in a vicious cycle.

Importantly, CPAP therapy has been shown to be an effective treatment for OSA in ESRD patients.[236] Though, OSA is thought to be underdiagnosed in kidney patients,[237] with the stereotypical sleep-related symptoms of OSA, namely snoring, witnessed apneas, nocturnal choking, and daytime sleepiness being reported less by CKD and ESRD patients.[238, 239] Further, while some investigators have found the traditional risk factors of aging, male gender, and obesity to be associated with OSA in CKD and ESRD populations,[43, 51, 235, 239-241] several others have found these associations to be weaker than in non-CKD populations indicating that the clinical presentation of OSA may be atypical in these populaitons.[38, 48, 239, 242-244]

Conversion of ESRD patients receiving thrice weekly conventional hemodialysis (CHD) to more intensive nocturnal hemodialysis (NHD) has been demonstrated to improve OSA.[50] Similarly, conversion from continuous ambulatory peritoneal dialysis (CAPD) to cycler-assisted nocturnal peritoneal dialysis (NPD) has been shown to reduce the frequency of OSA.[245] Several studies have also reported an improvement of OSA with renal transplantation,[246-249] though two studies found an improvement in only a minority of patients.[243, 250] High risk of OSA, as assessed by the Berlin Questionnaire,[251] has been found to be highly prevalent in the kidney transplant population[252] and was further found to be an independent predictor of graft loss among female kidney transplant patients.[253] However, it should be noted that the Berlin Questionnaire is not

interchangeable with objective monitoring[251] and has recently been shown to have low diagnostic accuracy in the CKD and ESRD populations.[254]

Pathogenesis

Both obstructive and central sleep apnea have been reported to occur in the CKD and ESRD populations.[43, 45, 50] This supports the hypothesis that the pathogenesis of sleep apnea in this population is due both to destabilization of central ventilatory control and upper airway occlusion. At present, there is a paucity of literature examining these relationships in CKD patients as previous studies have been confined to patients with ESRD or normal kidney function, though these same mechanisms may be occurring in patients with CKD. In ESRD, OSA severity has been reported to be positively correlated with enhanced ventilatory sensitivity,[242] which in turn destabilizes respiratory control by increasing loop gain.[127, 134] In brief, apneas occur when the respiratory drive is less than the threshold for inspiratory muscle activation and maintenance of upper airway patency during sleep. As the apnea progresses, respiratory drive increases until the threshold is passed and inspiration then occurs. If an overshoot in ventilation drives down carbon dioxide levels, the respiratory drive may again fall below the threshold for inspiration. As a result, the next apnea occurs from overcompensation of previous apnea. This 'loop gain' phenomenon has also been reported in OSA patients with normal kidney function.[255] Conversion of hemodialysis patients from CHD to NHD has been associated with decreased ventilatory sensitivity to hypercapnia, which correlated with a reduction in apnea severity.[256]

Alternatively, patients with CKD and ESRD may also develop OSA through mechanisms that promote upper airway occlusion during sleep. CKD and ESRD patients are vulnerable to fluid overload,[257-260] which predisposes them to pharyngeal narrowing as a result of interstitial

edema[261] and increased fluid volume in the neck and peripharyngeal structures.[262] Pharyngeal cross-sectional area has been reported to be decreased in ESRD patients compared to patients with normal kidney function.[263] Further, conversion of ESRD patients from CHD to NHD increased pharyngeal cross-sectional area and this increase was postulated to be a result of improved fluid removal.[264] Similarly, the improvement in peritoneal dialysis patients converted from CAPD to cycler-assisted NPD was associated with better fluid clearance and reduced pharyngeal narrowing, as measured by magnetic resonance imaging.[265] Displacement of fluid from the lower limbs has been reported to increase neck circumference and pharyngeal resistance[266] and reduce upper airway cross-sectional area.[267] This mechanism has been reported to contribute to the pathogenesis of OSA in patients with normal kidney function,[268] congestive heart failure,[269] and most recently, ESRD,[262] where a relationship between spontaneous rostral displacement of fluid from the lower extremities and the apnea hypopnea time was reported. Further, prevention of fluid accumulation in the legs during the day reduces nocturnal displacement to the neck and attenuates OSA in non-obese sedentary men.[270, 271] Interestingly, rostral fluid displacement increases upper airway collapsibility more in healthy non-obese men than women.[272] A similar relationship with gender has recently been reported in heart failure patients.[273] CKD patients are also prone to aldosterone excess,[190] which in the setting of high salt intake, has been hypothesized to contribute to OSA through increased sodium and water retention that promote tissue edema in the upper respiratory tract, leading to airway obstruction and worsening of OSA.[274] This is supported by studies which found plasma aldosterone levels to be correlated with OSA severity.[275, 276] Further, administration of an aldosterone (mineralocorticoid receptor) antagonist has been reported to reduce OSA severity in subjects with resistant hypertension.[277]

Another possible cause of pharyngeal narrowing in CKD and ESRD patients is upper airway dilator muscle dysfunction due to neuropathy or myopathy associated with chronic uremia or underlying diabetes.[45, 128] Muscle denervation[278] and sensory myopathy[279] have both been demonstrated in the upper airway of OSA patients with normal kidney function. These may further exacerbate the disease process in patients with CKD and ESRD.

OSA and the Kidney

OSA has been associated with abnormal renal histology, with the presence of glomerulomegaly and focal segmental glomerulosclerosis on human kidney biopsies of OSA patients.[26, 280] Previous studies have demonstrated an association between OSA and the presence of proteinuria,[26-34] while three smaller studies failed to confirm this association,[35-37] likely related to small sample sizes, variability in the definition and measurement of proteinuria and albuminuria, and lack of adjustment for confounders. However, several larger more recent cross-sectional studies have demonstrated a dose-response relationship between severity of OSA,[30, 34] nocturnal hypoxia,[32] and the degree of urinary albumin excretion. OSA increases the risk of hypertension,[9, 12, 23-25] stroke,[14, 93-95] and cardiovascular disease,[13, 18, 97-101, 233, 234], all of which are important and highly prevalent complications of CKD.[190] OSA may also accelerate the deterioration of kidney function in patients with CKD directly through the effect of hypoxia on the kidney.[52, 119, 120] Though cytoprotective in models of acute injury, up-regulation of hypoxia inducible factor (HIF) promotes fibrosis in experimental models of chronic renal injury.[281] The *'Chronic Hypoxia Hypothesis'* suggests that chronic ischemic damage in the tubulointerstitium of the kidney is the final common pathway in CKD for the development of ESRD.[119, 120] Alternatively, OSA may accelerate kidney function deterioration indirectly through increases in

systemic blood pressure,[282-285] inflammatory cytokines,[283, 286-289] and sympathetic nervous system activity.[290-293]

OSA and Altered RAS Activity

Increased RAS activity is associated with glomerular hyperfiltration (increased glomerular pressure), a precursor to kidney disease.[53, 294, 295] The *'Brenner Hypothesis of Glomerular Hyperfiltration'* states that maladaptive glomerular hemodynamic changes exert a major influence on the factors that initiate and perpetuate disease progression.[294, 295] These hemodynamic changes lead to glomerular hyperfiltration which in turn eventually result in progressive glomerular sclerosis and loss of kidney function.[294, 295] OSA patients have increased glomerular filtration compared to controls.[296] Further, indices of nocturnal hypoxemia were found to be associated with glomerular hyperfiltration.[296] Most importantly, treatment of OSA with CPAP therapy for one week resulted in a significant reduction in glomerular filtration.[296] The mechanism of this decrease in glomerular pressure remains unclear, however a sensitivity analysis stratifying patients based on those receiving RAS blockade therapy found that only those patients *not* receiving RAS blockade derived benefit from CPAP therapy,[296] thus implicating a role for the RAS in the pathophysiology of OSA and kidney disease.

Multiple lines of evidence link increased activity of the RAS with both initiation and progression of renal disease.[53] Angiotensin II (AngII), the effector molecule of the RAS, is a potent vasoconstrictor with pro-inflammatory effects.[297] In animal studies, chronic intermittent hypoxia (CIH) causes a progressive increase in blood pressure,[284, 285, 290-292, 298-302] mediated in part through renal sympathetic nerve activity that acts to increase RAS activity through upregulation of AngII type-1 (AT_1) receptors.[291, 292, 301, 302] Renal artery denervation, adrenal demedullation, and AT_1 receptor blockade with losartan ablate the increase in blood pressure in

response to CIH.[292, 301] Further, suppression of the RAS with a high-salt diet blocks the increase in blood pressure in rats exposed to CIH by suppressing kidney renin mRNA levels.[302] However, kidney AT_1 receptor expression was not affected, suggesting that the local tissue RAS may have a more primary role in mediating the increase in systemic blood pressure in response to CIH.[302] In humans, treatment with the AT_1 receptor blocker losartan ablates the rise in blood pressure in healthy men exposed to CIH.[303] Also, polymorphisms in the angiotensin-converting enzyme (ACE) gene modulate susceptibility to hypertension in sleep apnea.[304, 305]

Previous studies have reported that plasma levels of AngII[155, 306] and aldosterone[155] are increased in OSA patients compared to healthy controls, though one study found no acute overnight differences in plasma renin activity (PRA) and aldosterone levels between OSA patients and matched controls.[307] The prevalence of primary hyperaldosteronism has been reported to occur in 31% hypertensive OSA patients.[308] Plasma aldosterone levels have been correlated with OSA severity[275, 276] and administration of an aldosterone antagonist has been reported to reduce OSA severity in subjects with resistant hypertension.[277] In a non-controlled setting, OSA subjects demonstrated increased vascular sensitivity to intra-arterial AngII challenge (as measured by arterial forearm conductance) compared to healthy controls.[306] Finally, we have reported increased hemodynamic and aldosterone sensitivity to intra-venous AngII infusion, as well as impaired hemodynamic recovery, in OSA patients compared to healthy controls.[309]

Summary

The state of the science can be summarized as follows: OSA and nocturnal hypoxia are highly prevalent in the CKD[38-44] and ESRD[38, 42, 43, 45-50] populations and are strongly associated with both hypertension[9, 12, 19-25] and loss of kidney function.[52] Treatment of OSA with CPAP

significantly reduces glomerular filtration.[296] Though the mechanism remains unclear, we and others have shown that OSA is associated with altered RAS activity and sensitivity to AngII compared to healthy controls.[155, 296, 301-306, 308, 309] Whether treatment of OSA reverses or attenuates these phenomena remains unknown, hence the rationale for the current study.

OBJECTIVES

We sought to examine the effect of CPAP therapy on the physiologic and molecular responses to AngII challenge, a well-accepted measure of RAS activity,[310-325] as assessed by two means:

1. The changes in blood pressure (BP) in response to AngII infusion, pre- and post-CPAP therapy, in subjects with OSA.
2. The changes in circulating RAS components (PRA and aldosterone) in response to AngII infusion, pre- and post-CPAP therapy, in subjects with OSA.

HYPOTHESES

We postulated that RAS activity is altered in OSA subjects and that there would be a normalization of RAS activity with CPAP treatment for OSA. Specifically, we hypothesized that:

1. The blood pressure response to AngII challenge would be *less* sensitive post-CPAP compared to pre-CPAP therapy.
2. The PRA and aldosterone responses would be *less* sensitive post-CPAP compared to pre-CPAP therapy.

CHAPTER TWO: METHODOLOGY

Determination of OSA

Patients referred to the Foothills Medical Centre (FMC) Sleep Centre and Healthy Heart Sleep Company, in Calgary, AB, Canada, between June 2011 and May 2012, for suspected OSA performed an unattended, overnight cardiopulmonary monitoring study at home (Remmers Sleep Recorder Model 4.2, Saga Tech Electronic, Calgary, AB, Canada). The monitor consists of an oximeter to record oxyhemoglobin saturation (SaO_2) and heart rate variability, a pressure transducer to record nasal airflow, a microphone to record snoring, and a body position sensor. The oximeter provides the data for an automated scoring algorithm, which calculates the RDI based on the number of episodes of oxyhemoglobin desaturation ≥4% per hour of monitoring. Nocturnal oxygen saturation was sampled at 1 Hz. The Remmers Sleep Recorder has been validated by comparison to attended polysomnography.[60, 61] We defined sleep apnea as an RDI ≥15 as this reflects moderate to severe sleep apnea which is likely to be clinically significant.[60, 61] The Remmers Sleep Recorder has a sensitivity of 98% and specificity of 88% for a designation criterion of RDI ≥15.[61] Portable monitoring was performed following current guidelines and recommendations.[62-64] The raw data were reviewed by a blinded sleep medicine physician (PJH) who confirmed that the estimated RDI was accurate and determined whether apnea was central (Cheyne-Stokes respiration [CSR]) or obstructive (OSA), based on the morphology of the airflow recordings. Nasal pressure recordings with a characteristic crescendo/decrescendo pattern and no evidence of airflow limitation were classified as CSR, whereas recordings without a crescendo/decrescendo pattern and with airflow limitation were classified as OSA. Subjects with CSR did not qualify for this study and were excluded from recruitment. Additionally, subjects had to demonstrate significant nocturnal hypoxia, defined as an oxyhemoglobin saturation

(SaO_2) <90% for ≥12% of monitoring, which has been previously used in the Sleep Heart Health Study.[12]

Study Subjects

Men and women, age 18-70, with moderate to severe OSA (RDI ≥15) and significant nocturnal hypoxia (SaO_2 <90% for >12% of night) as diagnosed by a sleep medicine physician, were eligible to participate in the study subjects. Subjects underwent a medical history, physical examination, and laboratory screening. Exclusion criteria for the study included cardiovascular disease (symptoms consistent with myocardial ischemia, previously documented myocardial ischemia, cardiac arrhythmias or valve abnormalities, or abnormal echocardiogram at screening), cerebrovascular disease (transient ischemic attacks or stroke), kidney disease (eGFR<60 ml/min/1.73m^2 using the Chronic Kidney Disease Epidemiology Collaboration formula[184]), uncontrolled hypertension (BP>140/90 despite maximal use of antihypertensive medications), diabetes mellitus (defined by history, use of hypoglycemic agents or a fasting glucose >7mmol/L), severe lung disease (forced expiratory volume in one second / forced vital capacity ratio <70%), age <18 or >70, current treatment for OSA, current smoking, pregnancy, use of non-steroidal anti-inflammatory medications, oral contraceptives, inability to give informed consent, or at the discretion of the investigator. The study protocol was approved by the Conjoint Health Research Ethics Board at the University of Calgary. Written informed consent was obtained from all study subjects in accordance with the Declaration of Helsinki.

Study Protocol

The study protocol is well established and we have considerable experience with the methods (Figure 1).[310-325] Subjects were instructed to consume >200 mmol sodium per day for 3 days before each study day to ensure maximum RAS suppression.[302, 326] Subjects were studied in

the supine position in a warm, quiet room after an 8-hour fast. All subjects provided a second morning void spot urine for verification of diet compliance and determination of urinary sodium, potassium, and total protein excretion.[327] Subjects on medications which interfere with RAS activity were asked to discontinue their medications and switched to a calcium-channel blocker (amlodopine) at sufficient doses to achieve adequate blood pressure control two weeks prior to each study day, as these agents are considered to have a neutral effect on the RAS.[308]

At 8 am, an 18-gauge peripheral venous cannula was inserted into each antecubital vein (1 for infusion and 1 for blood sampling). After a 90 minute equilibration period BP, PRA, and aldosterone were measured at baseline and in response to 2 doses of Angiotensin II (3 ng/kg/min x 30 min and 6 ng/kg/min x 30 min) as an index of RAS activity. Investigation of the systemic responses to RAS activation by exogenously administered AngII allows for the examination of basal RAS activity.[310, 315, 316, 324] Blood samples were collected at baseline, after each AngII infusion, and after the 30 min recovery period. BP was recorded every 15 minutes by an automatic recording device (Dinamap; Critikon). Subjects were studied in the supine position using a standard cuff placed on the right arm. The mean of two readings taken by the same Registered Nurse (DYS) were recorded. Mean arterial pressure (MAP) was calculated as 1/3 systolic BP (SBP) + 2/3 diastolic BP (DBP).

CPAP Treatment

After completing the first study day, subjects were treated with CPAP therapy, as per the guidelines for treatment of OSA, for at least 1 month once adequate therapy has been achieved (Figure 2).[55] Adherence to CPAP therapy was monitored by electronic download of CPAP use from the unit each month. Once satisfactory CPAP adherence was achieved (defined as CPAP use for >4hrs/night for 1 month)[55] and correction of OSA and nocturnal hypoxia has been

confirmed by a repeat ambulatory cardio-pulmonary monitoring while using CPAP and reviewed by a sleep medicine physician (PJH), subjects underwent an identical study day.

Laboratory Measurements

A radioimmunoassay (RIA) was utilized for PRA (DiaSorin Clinical Assays, Stillwater, MN, USA). In brief, Angiotensin I (AngI), the primary product of PRA was generated at 37°C from endogenous renin and renin substrate at pH 6.0. The integrity of the generated AngI was maintained by inhibition of proteolytic activity using EDTA and phenylmethylsufonyl fluoride in the generation system. The accumulated AngI reflects PRA under these controlled conditions. The AngI generated was determined by RIA using competitive binding principles, where the antibody was immobilized onto the lower inner wall of coated tubes. Aldosterone was also measured using an RIA assay. AngII plasma levels were measured by standard laboratory immunoassay techniques (Quest Diagnostics; San Juan Capistrano, CA, USA). Urinary total protein excretion was determined by a turbidimetric endpoint assay using benzethonium chloride (Roche Total Protein Urine/CSF Gen. 3, Roche). Urinary sodium and potassium were determined by an indirect potentiometry assay using an ion-selective electrode (Roche Cobras Integra Sodium, Roche). Fasting glucose was determined by a hexokinase-UV assay. 25'OH Vitamin D was measured using the Liaison® 25'OH Vitamin D Total assay which uses chemiluminescent immunoassay technology for the quantitation determination of 25-hydroxyvitamin D and other hydroxyla.

Sample Size

The primary outcomes of interest outlined in this thesis are part of a study originally designed to examine the effect of CPAP therapy on RAS activity in the kidney. As such, the sample size is based on a renal outcome (filtration fraction [FF]). We calculated that 12 subjects

would be required to detect a 3% *difference* in the FF response to AngII infusion before and after OSA treatment with CPAP using 80% power and an alpha of 0.05. This estimate is based on data from Miller et al who demonstrated a difference of 3±1% in the FF in response to AngII infusion after RAS blockade with the AT_1 receptor blocker (ARB) irbesartan, as compared to before RAS blockade, on a high-salt diet in healthy Caucasians.[318] Higher measures of FF can be interpreted as greater glomerular capillary pressure, which cannot be measured directly in humans, and is a precursor to glomerulosclerosis and ultimately, kidney failure.[294, 328, 329] Importantly and underscoring the clinical importance of FF, a study of kidney transplant recipients found that for every 1% increase in FF, there was a 3% increase in having overall graft loss per year.[328]

Analysis

Data are reported as mean ± standard error (SE), number (percentage), or median (range), where appropriate. Our primary outcomes were the changes (Δ) in BP, PRA, and aldosterone at baseline and in response to AngII (3 ng/kg/min, 6 ng/kg/min, and recovery), as a measure of RAS activity, pre- and post-CPAP therapy for OSA. Pre- and post-CPAP comparisons were made using the Wilcoxon Sign-Rank Test (non-parametric t-test). The Friedman Test was used to ensure an appropriate vasoconstrictor response to AngII infusion was observed on each study day. Missing data were carried forwards or backwards, assuming no change, where appropriate. All statistical analyses were performed with statistical software package SPSS V.17.0 (SPSS, Chicago, IL, USA) and were 2-tailed with a significance level of 0.05.

CHAPTER THREE: RESULTS

Study Enrollment

Twelve OSA subjects completed the study and were included in the final analyses. One subject ingested 1 dose of the ARB candesartan the morning of the first study day; this subject was studied in an identical fashion post-CPAP therapy to allow for comparison of pre-post CPAP results in an identical setting. This subject was included in the primary analyses, but excluded in a sensitivity analysis.

Baseline Characteristics

Subject characteristics are presented in Table 1. Twelve newly diagnosed (10 men and 2 post-menopausal women; mean [SE] age 51 [33, 68] years) OSA subjects (RDI $\geq$15) with nocturnal hypoxia (SaO_2 <90% for >12% of night) were recruited into the study. All had BP <140/90 mmHg (5 subjects on antihypertensive medication) and were free of RAS-interfering medications. All subjects were non-diabetic, non-smoking, and in high-salt balance, a state of maximal RAS suppression, as indicated by urinary sodium excretion. Additionally, all subjects had normal kidney function (eGFR $\geq$60 mL/min/1.73m^2) and urinary total protein excretion (<200 mg/day) as defined by National Kidney Foundation guidelines,[1] with the exception of 1 subject who had increased urinary total protein excretion (UTPE, 341 mg/day).

As anticipated, all subjects demonstrated significant changes in all indices of blood pressure ($p<0.001$), PRA ($p<0.001$), and aldosterone ($p<0.001$) in response to AngII challenge compared to baseline values (pre-CPAP therapy).

CPAP Therapy

All subjects responded to CPAP therapy. CPAP treatment (median [range], 94 [62, 260] days) reduced the RDI and improved indices of nocturnal hypoxia (Table 1). A download of

CPAP compliance for the last 30 days prior to the post-treatment study day revealed that CPAP was used 94±4% of nights (mean [SE], 79±7% with usage >4 hours/night), with an average nightly usage of 6.3±0.6 hours, indicating adequate CPAP compliance.

Pre- vs. Post-CPAP Therapy

Baseline Characteristics

There were no differences in terms of fasting glucose, Vitamin D, or urinary sodium and potassium excretion post-CPAP therapy (Table 1). CPAP therapy resulted in a large reduction in UTPE in all subjects (Figure 3). There was also a non-significant reduction in baseline heart rate and a non-significant increase in BMI post-CPAP.

As anticipated, all subjects demonstrated significant changes in all indices of blood pressure ($p<0.001$), PRA ($p<0.001$), and aldosterone ($p<0.001$) in response to AngII challenge compared to baseline values (post-CPAP therapy).

Blood Pressure

Changes in baseline BP are reported in Table 1. CPAP treatment reduced baseline MAP and DBP. There was also a non-significant reduction in baseline SBP.

Study subjects' BP responses to AngII challenge are reported in Table 2. Study subjects demonstrated increased MAP sensitivity to AngII at 15 minutes post CPAP-therapy (Figure 4). There were also non-significant increases in MAP sensitivity to AngII at 30 and 45 minutes post-CPAP therapy. There were no differences in the MAP sensitivity to AngII at 60 minutes or after the recovery period. The MAP response was driven primarily by the DBP response to AngII, which followed a similar pattern (Figure 5). There were also non-significant increases in SBP sensitivity to AngII infusion at 15 and 45 minutes post-CPAP therapy, though there were no differences in sensitivity at 30 and 60 minutes or after the recovery period (Figure 6).

Circulating RAS Components

Baseline circulating RAS components pre- and post-CPAP therapy are reported in Table 1. CPAP treatment decreased circulating aldosterone levels in 11 out of 12 subjects (Figure 7), but did not alter circulating AngII levels. There was also a non-significant decrease in PRA (Figure 8) post-CPAP therapy, which occurred in 9 out of 12 subjects. Two subjects had large increases in PRA, while 1 subject remained unchanged. Interestingly, hypoxia was not fully corrected in these 3 subjects, though the hypoxia pattern was noted to have changed from an intermittent to a more sustained pattern.

Changes in PRA and aldosterone sensitivity to AngII are reported in Table 2. There were no significant differences in PRA response to AngII infusion after CPAP therapy, though the PRA responses did appear to be blunted post-CPAP therapy (Figure 9). Conversely, there were no significant differences in the aldosterone sensitivity to AngII after CPAP therapy, though the aldosterone response did appear to be more sensitive post-CPAP (Figure 10). There was also a non-significant blunting in the aldosterone recovery post-CPAP therapy.

Sensitivity Analyses

A sensitivity analysis excluding the subject who violated the study protocol by taking candesartan did not alter our results. Exclusion of the two female subjects did not alter our primary findings, though the non-significant increases in BP sensitivity to AngII at 30 minutes (post-CPAP therapy) became significant (MAP, $p=0.022$; SBP, $p=0.032$; DBP, $p=0.036$). Similarly, the non-significant blunting in the aldosterone recovery post-CPAP therapy also became significant ($p=0.019$). A sensitivity analysis removing the subject who still demonstrated significant nocturnal hypoxia post-CPAP therapy (SaO_2<90% for 31% of night) resulted in decreased baseline PRA ($p=0.050$) and increased BP sensitivity to AngII at 30 minutes (MAP,

p=0.031; SBP, p=0.119; DBP, p=0.021). There was also a non-significant increase in BP sensitivity to AngII at 45 minutes (MAP, p=0.11; SBP, p=0.083; DBP, p=0.091). Additional exclusion of the 2 subjects in whom hypoxia was partially corrected (9.2% and 8.3%) resulted in further decreases in baseline SBP (p=0.012) and PRA (p=0.021) and significant increases in BP sensitivity to AngII at 45 minutes (MAP, p=0.038; SBP, p=0.024; DBP, p=0.065). Our other findings remained unchanged with exclusion of the subjects with partially corrected hypoxia. Finally, exclusion of the 5 subjects with controlled hypertension did not significantly alter our results.

CHAPTER FOUR: DISCUSSION

Primary Findings

We examined RAS activity in humans with OSA before and after CPAP therapy. To our knowledge this is first study to examine the effect of CPAP treatment on the hemodynamic and circulating RAS component responses to an AngII challenge, a well-accepted indirect measure of RAS activity.[310-325] Our primary findings were that treatment of OSA with CPAP resulted in: (1) decreased baseline blood pressure and increased hemodynamic sensitivity to AngII; (2) decreased PRA (hypoxia corrected subjects only) and aldosterone levels at baseline, but did not affect PRA or aldosterone sensitivity to AngII; and (3) decreased urinary protein excretion. These findings suggest that RAS activity is down-regulated in OSA subjects treated with CPAP, supporting a role for the RAS in mediating OSA-induced hypertension in humans.

Treatment of OSA with CPAP and the RAS

Several studies have examined the effect of CPAP therapy on components of the RAS. Follenius et al reported that one night of CPAP therapy increased PRA and aldosterone levels.[330] Saarelainen et al reported a decrease in plasma aldosterone but no change in renin in 11 male hypertensive subjects without other co-morbidities after 3 months of CPAP treatment.[331] Meston et al conducted a randomized control trial in 101 male subjects with OSA.[332] Subjects were randomized to therapeutic or sham CPAP. The authors reported no differences in renin levels post-CPAP therapy but equivalent increases in aldosterone levels after 1 month.[332] Moller et al administered CPAP to 13 OSA patients for 14 months and found no statistically significant reductions in renin or angiotensin II.[155] However, CPAP therapy reduced BP, and the reduction in BP was correlated with a decrease in both plasma renin and AngII concentrations.[155] Svatikova et al compared aldosterone and renin levels in 21 OSA patients without co-existent

cardiovascular disease to those of similarly obese healthy control subjects.[307] They authors found that neither OSA nor CPAP treatment acutely affected overnight plasma aldosterone or renin levels.[307] Finally, the forearm vasoconstrictor response to an intra-arterial AngII infusion has been reported to be increased in normotensive patients with OSA.[306] These studies differ with varying sample sizes and intervention periods, and are limited because they included only male subjects, did not quantify or examine the hypoxia profile of their subjects, and most importantly, a majority did not control for salt intake, kidney function, or other factors known to affect the RAS. Hence, the mechanistic relationship between OSA and the RAS in patients without co-morbidities aside from OSA remains unclear.

Our study addresses several of the limitations of these previous studies. We included women, subjects with significant nocturnal hypoxia, and controlled for factors known to affect the RAS. Previous studies examining the effect of CPAP therapy on BP have shown different results ranging from no significant changes[333-336] to almost a 10 mmHg decrease,[114, 139, 140, 144-156] with meta-analyses reporting a decrease in BP of -1.4 to -2.5 mmHg.[337-339] The large variation in findings likely reflects differences in baseline hypertension, use of antihypertensive medications, treatment length, CPAP adherence, presence of co-morbidities, and the severity of OSA and/or hypoxia. We observed a large BP reduction (-6 mmHg for MAP, SBP, and DBP) similar to several previous studies,[146, 151, 154, 155] which likely reflects the healthiness of our study population. We also observed reductions in baseline PRA, aldosterone, and UTPE levels with CPAP treatment, though the reduction in PRA was only present in those subjects in whom the hypoxia component was corrected. We have previously reported that OSA subjects have increased hemodynamic and aldosterone sensitivity to infused AngII, as well as impaired hemodynamic recovery, compared to healthy controls.[309] Consequently, we hypothesized that the

hemodynamic and circulating RAS component responses to an AngII infusion would be less sensitive following CPAP therapy. However, contrary to our hypotheses, we found that the hemodynamic sensitivity to infused AngII was enhanced with CPAP therapy. Further, despite reductions in baseline circulating PRA and aldosterone levels post-CPAP therapy, OSA subjects treated with CPAP demonstrated a similar circulating PRA and aldosterone sensitivity to infused AngII. However, the shifts in the PRA and aldosterone response curves are likely beneficial as they minimize the potentially harmful effects of an activated RAS.

Mechanisms of Action

Intermittent hypoxia is thought to lead to increased oxidative stress, systemic inflammation, and sympathetic activation, which in turn induce endothelial dysfunction.[136, 183] Accordingly, there are several mechanisms which may account for the increased hemodynamic sensitivity to infused AngII in OSA subjects. Increased hemodynamic responsiveness to AngII may be the result of alterations and vascular remodelling of the arterial wall.[306] In particular, an increased wall-to-lumen ratio generates a greater force and thus enhanced resistance increase at a greater concentration of vasoconstrictor.[340] Nocturnal BP surges[341] inherent to OSA[342] and increased permanent or nocturnal release of norepinephrine,[343] thromboxane A_2,[344] and/or endothelin[345] may promote long-term vascular growth resulting in greater hemodynamic sensitivity in OSA subjects. Animal studies demonstrating increased RAS activity as a consequence of increased sympathetic tone during CIH support an increased growth-promotive influence on the vessel walls in OSA. [346]

The greater hemodynamic sensitivity during AngII infusion may also reflect increased sensitivity of the vessel walls to vasoconstrictors at the cellular level.[306] Altered endogenous RAS activity seems the most likely explanation for our findings. Animal studies have

demonstrated that exposure to CIH causes an increase in BP mediated through sympathetic activation which acts to increase RAS activity through upregulation of the AT_1 receptors.[291, 292, 301, 302] Indeed, altered levels of any of the individual components of the circulating and local tissue RAS, including PRA, AngII, aldosterone, the AT_1 and mineralocorticoid receptors, angiotensin-converting enzyme, the initial substrate angiotensinogen, and/or other components of the RAS could promote a greater hemodynamic sensitivity to AngII. The finding of augmented hemodynamic sensitivity to infused AngII has been reported previously in users of the oral contraceptive (OC).[347] Ahmed et al found the hemodynamic response to infused AngII was significantly augmented in OC users compared to non-users despite similar baseline blood pressures.[347] This was associated with increased AT_1 receptor mRNA expression, suggesting that AT_1 receptor downregulation was not the mechanism responsible for the maintenance of normal hemodynamic function in OC users.[347] Further, our subject who ingested candesartan demonstrated a response to AngII despite AT_1 receptor blockade, providing evidence for AT_1 receptor up-regulation in humans with OSA. Alternatively, parts of the constrictive action of AngII could be explained by augmented pre-synaptic release of norepinephrine[348] or other vasoconstrictors, such as free oxygen radicals,[349] reduced reuptake of catecholamines,[350] and facilitation of the vasoconstrictive effect of sympathetic activation.[351] Thus, enhanced vasoconstriction in OSA subjects is likely a consequence of increased sympathetic tone, a well-known characteristic of OSA.[352, 353]

Another possible mechanism for the augmented hemodynamic response to AngII observed in OSA subjects is dysfunction of the nitric oxide (NO) system. AngII-induced vasoconstriction is normally attenuated by the concomitant release of NO via shear stress-dependent and -independent pathways.[349] Therefore, enhanced vasoconstriction during AngII

infusion in OSA may also be the result of reduced coactivation of endothelial NO synthesis or increased NO degradation accompanying the activation of NO synthesis.[306] In a follow-up to the previously described OC user study, Cherney et al found that the hemodynamic response to L-arginine infusion was blunted in OC users compared to non-users, suggesting increased NO system activity in OC users, and that further delivery of the substrate for endothelial NO synthase (eNOS) could not overcome the hemodynamic effects of ongoing OC-induced RAS activation.[354] This finding was supported by tissue eNOS mRNA levels.[354] OSA subjects have been reported to have reduced levels eNOS and more importantly, CPAP treatment has been reported to increase eNOS levels.[170] Alternatively, reduced recruitment of other counter-regulatory vasodilators may be the result of a diminished effect of AngII type-2 (AT_2) receptors,[355] which have been proposed to mediate NO release,[356] aortic but not vascular cyclic GMP production,[357, 358] and vasodilation.[359] Downregulation of AT_2 receptors or disruption of post-AT_2 receptor signal transduction is another possible mechanism explaining the increased hemodynamic sensitivity in OSA.[306] Further, the release of norepinephrine, which is increased in OSA,[343, 352, 360] downregulates AT_2 receptor expression in cardiac myocytes,[361] providing some support for this mechanism. Finally, the net effect of endogenous vasodilators, such as NO, on the extent of induced vasoconstriction by vasoconstrictors, such as AngII, may be nullified by prevailing neurohumoral and/or paracrine vasoconstrictor overweight.[306] As such, the increased sensitivity to AngII in OSA may be the result of a shifted balance between endogenous vasoconstrictors[345, 352, 360] and vasodilators[349] to a higher level of activity, exhausting the ability of vasodilatory mechanisms to counteract further vasoconstrictive challenges.[362]

It is likely that each of the aforementioned mechanisms have some role in mediating the altered RAS activity observed in OSA subjects; though it remains unclear which mechanisms are

the most important. Contrary to our hypothesis, we found that CPAP therapy increased the hemodynamic sensitivity to infused AngII. This occurred despite decreases in baseline BP and circulating levels of PRA and aldosterone, though circulating levels of PRA and aldosterone may not necessarily reflect local tissue RAS levels.[302] A high-salt diet is known to suppress RAS activity to basal levels.[302, 326] However, in animals exposed to CIH, kidney AT_1 receptor expression has been shown to be unaffected by high-salt diet, suggesting that the local tissue RAS may be more important in mediating systemic BP.[302] Our results indicate that CPAP therapy downregulates many components of the RAS, though whether AT_1 receptor expression is affected remains unclear. We speculate that the number of AT_1 receptors remained unchanged post-CPAP therapy and that a decrease in the levels of various RAS components may have left more AT_1 receptors available for activation. Consequently, when AngII was infused, there was an augmented hemodynamic response. Our subject who ingested candesartan demonstrated an augmented hemodynamic response post-CPAP therapy, despite AT_1 receptor blockade and decreased circulating PRA and aldosterone levels, providing support for this theory. This effect could also be the result of a change in some other unmeasured or unknown component of the RAS or vasculature. The role of the mineralocorticoid (aldosterone) receptor in OSA also remains unclear, though there is some evidence suggesting that it may be up-regulated in OSA.[275-277] Certainly, one could speculate that a similar mechanism to that described for the AT_1 receptor above may also apply to the mineralocorticoid receptor. We found no difference in the aldosterone sensitivity to infused AngII, though there was a non-significant impairment in the aldosterone recovery. This implies that although basal circulating aldosterone levels were reduced by CPAP therapy, adrenal gland sensitivity to AngII was not affected, resulting in a similar increase in circulating aldosterone levels. The impaired recovery of circulating

aldosterone supports the theory of mineralocorticoid receptor downregulation with CPAP therapy. In response to AngII, the reduced number of receptors would become saturated with the excess aldosterone released by the adrenal gland, resulting in a delayed usage of the accumulated aldosterone and therefore an impaired recovery. Conversely, circulating PRA demonstrated a non-significant blunting and improved recovery to infused AngII, though this was likely due to the decrease in baseline PRA. We also observed no difference in the hemodynamic recovery to infused AngII post-CPAP therapy, despite there being an augmented sensitivity, though numerically the recovery did appear to be improved with CPAP treatment. This suggests that there was an improvement in some vasodilatory compensatory mechanism, possibly mediated through the NO system or AT_2 receptor, though our study was not designed to assess these mechanisms. Finally, it is important to remember that subjects with OSA are often unknowingly exposed to the deleterious consequences of OSA for years. It therefore would not be surprising that in response to CPAP therapy there is ongoing vascular remodelling and that our intervention period was likely not sufficiently long enough to capture all of these important changes.

Clinical Implications

Urinary Protein Excretion

The reduction in urinary protein excretion after CPAP therapy also merits discussion. Several previous studies have demonstrated an association between OSA and/or nocturnal hypoxia and the presence of proteinuria,[26-34] though three smaller studies failed to confirm this association.[35-37] At present only two small case studies have examined the effect of CPAP on proteinuria.[27, 28] Both have reported significant reductions and a reversal in proteinuria.[27, 28] We extend these findings by showing a reduction in UTPE in all 12 subjects after 1 month of adequate CPAP therapy. Proteinuria, even within the normal range, is a powerful predictor and

potential contributor to cardiovascular events,[192-204] CKD progression,[198, 199] ESRD,[198, 199, 205, 206] and all-cause mortality,[193, 195, 197-199, 202, 207] though the role of proteinuria and its primary component albuminuria in the pathophysiology of these conditions remains elusive. Numerous studies have suggested that only neglible amounts of albuminuria should be considered normal.[192, 196, 203] Reductions in albuminuria and proteinuria by means of RAS blockade have been associated with improved renal[363-366] and cardiovascular[194, 201, 203] outcomes, though it remains unclear if albuminuria and proteinuria are surrogate endpoints for cardiorenal disease and thus potential therapeutic targets or simply biomarkers.[367] We have previously reported increased UTPE, within the normal range, to be associated with up-regulated vascular RAS activity and a blunted DBP response to infused AngII, in healthy humans.[313] Interestingly, in the present study, we observed a reduction in UTPE and an augmented DBP response to AngII following CPAP, further supporting the relationship between UTPE and the RAS. AngII, the effector molecule of the RAS, has pro-inflammatory effects.[297] This increased inflammation, coupled with the augmented intraglomerular pressure and resulting increased local leakage of albumin[368] attributed to up-regulated RAS activity, may contribute to widespread vascular permeability even in healthy subjects,[369-371] underscoring the plausibility of this pathophysiological relationship. Further, the AT_1 receptor has been implicated in pathways known to cause endothelial damage such as synthesis of interleukin-6[372] and generation of reactive oxygen species,[373] which damage the glomerular filtration barrier. Conversely, urinary albumin has been demonstrated to stimulate the RAS in proximal tubular cells.[374] Alternatively, the observed reduction in UTPE may be a systemic or renal hemodynamic effect, with the reduction in UTPE being a result of a decrease in blood pressure or glomerular filtration.

Regardless of the mechanism, a reduction in UTPE occurred in all OSA subjects treated with CPAP and should be an important area of future study.

Blood Pressure

Hypertension is the most important risk factor contributing to mortality worldwide,[375] though its determinants remain poorly understood. OSA is an independent risk factor for the development of hypertension.[9, 12, 23-25] During the OSA cycle BP can vary by more than 50 mmHg in a period of 10 to 15 seconds.[376] Every 20 mmHg increase in SBP (10 mmHg increase in DBP) doubles the risk of cardiovascular disease.[377] Among patients less than 65 years old, there is a progressive increase in the risk of stroke and coronary disease with increasing BP.[378] In individuals over age 65, the risk continues to increase with rising SBP, but a reversal occurs with the DBP; the lower the DBP at a given SBP, the greater the risk.[379] Consequently, an increased pulse pressure (PP, SBP-DBP) is associated with an increased risk for adverse events.[379] The Framingham Heart Study found DBP to be the strongest predictor of coronary heart disease in patients <50 years of age.[380] Further, age 50 to 59 years was a transition period when SBP, DBP, and PP were comparable predictors, and from 60 years of age on, DBP was negatively related to coronary heart disease risk so that PP became superior predictor to SBP.[380] Given that the average age of our study population was 51, with a majority of subjects being <60 years of age, it is perhaps not unexpected that the most significant hemodynamic changes post-CPAP therapy were with DBP in our study population. Antihypertensive therapy has been associated with a 35-45% reduction in stroke, 20-25% decrease in myocardial infarction, and >50% reduction in heart failure.[381, 382] In 17 control trials, a 5-6 mmHg reduction in DBP has been associated with a 16% reduction in the number of coronary events and a 40% reduction of stroke.[382] Further, a 10 year 12 mmHg decrease in BP results in the prevention of 1 death for every 11 patients treated.[383]

Aldosterone

There is growing recognition of the consequences of increased aldosterone secretion and its contributions to hypertension.[274, 276, 277, 308, 384-388] Treatment with aldosterone (mineralocorticoid receptor) antagonists reduces morbidity, mortality, and hospitalizations in patients with hypertension and systolic heart failure.[384-386] In recognition of these findings, the most recent Canadian Hypertension Education Program guidelines have recommended the use of mineralocorticoid receptor antagonists in addition to traditional RAS-interfering medications in patients with hypertension and systolic heart failure.[389] The results from the present study suggest that CPAP therapy may also be effective at lowering circulating aldosterone levels.

OSA and CPAP

OSA increases the risk of hypertension,[9, 12, 23-25] stroke,[14, 93-96] cardiovascular disease,[13, 18, 97-102] and both cardiovascular[105-107] and all-cause mortality.[105, 107-111] OSA also causes excessive daytime sleepiness, inattention, fatigue, and impairment of sleep quality,[55, 72] which in turn impair daytime and neurocognitive function,[73-76] diminish quality of life,[77] and increase the likelihood of errors,[73, 74] motor vehicle[78-85] and occupational[86, 87] accidents. CPAP therapy reduces respiratory events and hypoxia during sleep,[135, 137-139] daytime sleepiness,[75, 139-143] blood pressure,[114, 139, 140, 144-156] hospitalizations,[157] MetS,[114] cardiovascular events,[13, 106, 158] motor vehicle accidents, [79, 80] and mortality,[106, 107, 159, 160] while concomitantly improving quality of life[75, 139] and cognition.[75, 161] CPAP therapy is cost-effective[80, 162-166] and the number needed to treat to prevent 1 cardiovascular event in 10 years is 3.5.[158] Importantly, discontinuing CPAP for even 1 night may mitigate the benefits of CPAP.[139, 181-183] However, approximately 30% of patients with OSA do not tolerate CPAP[390, 391]and an even higher number do not use their CPAP for the entire night.[182, 392-398] Approximately 46-83% of patients are defined as non-adherent

when adherence is defined as >4 hours of use per night.[393] There is no consensus regarding the duration of nightly usage that is necessary to experience the maximum benefits of CPAP, though several studies have suggested that usage >6 hours per night is necessary for optimal benefit.[142, 143, 161]

CPAP versus RAS Blockade

Given that OSA is associated with altered RAS activity, [155, 296, 301-306, 308, 309] our present finding that RAS activity is down-regulated with CPAP therapy, and the widespread issues with CPAP tolerance and adherence,[182, 390-398] the option to treat OSA patients with a RAS-inhibiting medication may be worthwhile. Currently, it remains unclear whether CPAP therapy or RAS blockade is the most beneficial to patients with OSA. Administration of the aldosterone antagonist spironolactone for 8 weeks has been reported to attenuate OSA severity by ~50% in subjects with resistant hypertension.[277] However, RAS blockade does not mitigate the daytime symptoms of OSA, whereas CPAP therapy effectively reduces daytime sleepiness[75, 139-143] and improves both cognitive function[75, 161] and quality of life.[75, 139] Our study subject who ingested candesartan provides additional insight. This subject was found to have large reductions in BP, PRA, aldosterone, and UTPE post-CPAP therapy, while demonstrating increased hemodynamic sensitivity to infused AngII, suggesting that CPAP treatment provides an additional benefit beyond RAS blockade. This concept is further supported by a randomized control crossover trial of 23 subjects with untreated hypertension and OSA.[152] Subjects were randomized to the ARB valsartan (160 mg/day) or CPAP therapy.[152] Though, there were significant reductions in mean 24-hour BP with both CPAP and valsartan treatment, valsartan induced a fourfold higher decrease in mean 24-hour BP than CPAP.[152] More importantly, an extended trial of treatment that combined the 2 therapies showed further significant reductions in BP,[152] highlighting the

potential benefits of dual therapy. Finally, it is important to consider cost when contemplating whether to utilize CPAP or RAS blockade therapy, as treatment of OSA will likely be a lifelong requirement. CPAP therapy has a higher initial set-up cost, though this need only be done once, whereas RAS-interfering medications have lower costs but prescriptions require frequent refills.. Consequently, RAS blockade therapy may result in higher long-term costs. Based on the evidence, CPAP therapy should be used when possible to treat OSA.[54, 55, 59, 127, 135] In patients where CPAP treatment is not a possibility, consideration should be given to prescribing an RAS-interfering medication.[277] Concomitant CPAP and RAS blockade therapy is likely of further benefit[152] and will be an important area of future study.

Strengths and Limitations

Our study has several strengths. We utilized a well-accepted measure of RAS activity[310-325] and controlled for factors known to affect the RAS. All subjects had newly diagnosed and untreated moderate to severe OSA with marked nocturnal hypoxia, suggesting that any of the effects of OSA and CPAP therapy on the RAS should have been most evident in our study population. We included only subjects with a BP <140/90 who had no other coexisting diseases and were in general free of RAS-interfering medications. The pre-post study design allows us to comment on causality and to assess the effect of CPAP on RAS activity independent of age, gender, obesity, and other residual confounders, as these factors should have been identical on both study visits. Further, we included women and subjects with controlled hypertension, thereby increasing the generalizability and clinical implications of our results.

Notwithstanding these strengths, our study has limitations. First, our study sample was limited to OSA subjects who were non-diabetic, non-smoking, with BP<140/90, normal renal function, and the absence of co-morbid disease, limiting the generalizability of our study results

to OSA populations with a greater burden of co-morbid disease. However, by studying a healthier population of OSA subjects, we aimed to examine the impact of CPAP therapy on BP and circulating RAS components without any confounding factors. Further, by design, we included only subjects with both moderate to severe OSA and significant nocturnal hypoxia. Consequently, it remains unclear whether it is the treatment of apneas or intermittent hypoxia that is responsible for our findings. Certainly, our sensitivity analyses excluding the subjects with partially corrected hypoxia suggests that treatment of intermittent hypoxia provides additional benefit to RAS activity. Second, we attempted to minimize the effect of sample size and intraindividual variability by utilizing a homogenous study group and careful pre-study design. We ensured that all participants were ingesting similar amounts of salt to ensure maximum RAS suppression[302, 326] and that all subjects were free RAS-interfering medications and hormone replacement therapy. In addition, all subjects were studied at the same time of the day, while resting in the supine position in a warm, quiet room after an 8-hour fast. We also enrolled healthy subjects free of kidney disease, diabetes, cardiovascular disease, and smoking, as these conditions can influence RAS activity. Third, as it is not possible to measure vascular RAS activity directly in humans, we utilized the well-accepted method of indirectly measuring the RAS in humans by observing the response to AngII challenge.[310-325] Fourth, a spot urine was used for determination of sodium, potassium, creatinine, and protein excretion in place of the gold standard 24-hour urine sample; however, even in the most careful of research settings, 24-hour urine collections are prone to error and there is excellent correlation between spot morning urine samples and 24-hour urine collection for estimation of albumin and protein excretion.[399] Fifth, we used portable monitoring in place of polysomnography for diagnosing OSA and evaluating CPAP treatment. However, portable monitoring was performed in a population at

high risk for OSA following current guidelines and recommendations[62-64] and analyzed by a sleep medicine physician. Finally, the length of the treatment period was likely insufficient to demonstrate the full benefits of CPAP therapy on RAS activity as OSA patients are often unknowingly exposed to the deleterious consequences of OSA for years. Though given that we did find an improvement in RAS activity, this suggests that changes in RAS activity in response to CPAP occur as early as 1 month and are likely ongoing.

Future Directions

There are several aspects of this research which merit future study. It would be interesting to examine the long term effects of CPAP therapy on the RAS and kidney function, as vascular remodelling is likely ongoing. With a larger sample size, it would be interesting to conduct stratifications based on age, gender, and hypertension status to examine whether these entities modify the effect of CPAP therapy on the RAS. We have also been collecting samples for the determination of renal hemodynamics, which will eventually provide direct insight as to the effect of CPAP therapy on kidney function and the renal RAS. It also remains unclear whether it is apneas per se, hypoxia, or both of these factors together that are responsible for the altered RAS activity in OSA. This could be examined by studying subjects with OSA but no hypoxia or subjects with hypoxia but no OSA. Further, it would be interesting to utilize a healthy human model to examine the effect of intermittent hypoxia exposure on the RAS. Alternatively, one could examine the effects of other models of acute and chronic hypoxia on the RAS, such as the hypoxia experienced at altitude or with chronic obstructive pulmonary disease. The effect of supplemental oxygen therapy, which may be better tolerated, could be an alternative to CPAP therapy, though the effect of supplemental oxygen on the RAS and kidney has not been studied to date. The role of the NO and AT_2 receptor pathways in OSA is another area requiring further

study. Finally, the role of RAS blockade in both OSA and CPAP therapy remains unclear and requires further elucidation. Given the present findings, future studies should be undertaken to examine the acute and chronic effects of RAS blockade in OSA subjects in the context of concomitant CPAP therapy.

Conclusions

RAS activity is altered in OSA and improved by CPAP therapy. In OSA subjects who were otherwise well, we found CPAP therapy to down-regulate RAS activity through decreases in blood pressure, circulating RAS components, and urinary protein excretion, and increased hemodynamic sensitivity to infused AngII. These findings are important given the increasing prevalence of OSA and high impact on cardiovascular morbidity[13, 18, 97-102] and mortality,[105-107] quality of life,[77] and health care costs.[14, 96, 102, 111, 124, 133] OSA represents a significant burden to the health-care system that can be effectively treated with CPAP therapy.[54, 55, 59, 127, 135] Concomitant RAS-inhibition and CPAP therapy may also provide additional benefit to patients with OSA. Further studies are required to confirm our findings and to better elucidate the role of the RAS in the development of OSA-mediated hypertension, cardiovascular, and kidney disease.

Table 1: Baseline Characteristics

Parameter	Pre-CPAP	Post-CPAP	P-value
Age, years	51±3	-	-
Gender, N (% Male)	10 (83)	-	-
Race, N (% Caucasian)	7 (58)	-	-
BMI, kg/m^2	32±1	33±1	0.075
eGFR, $ml/min/1.73m^2$	99±4	-	-
Fasting glucose, mmol/L	4.7±0.2	4.7±0.1	0.88
25'OH Vitamin D, nmol/L	65±7	72±7	0.27
Heart Rate, bpm	69±3	65±3	0.11
Urinary Na+, mmol/day	367±27	369±54	0.31
Urinary K+, mmol/day	87±3	90±7	0.81
UTPE, mg/day[†]	69 (39, 341)	48 (22, 204)	0.002
RDI, hr^{-1}	58.6±5.4	4.7±0.8	0.002
SaO_2<90, %	35.2±5.1	5.0±2.6	0.002
Mean SaO_2, %	90.2±0.6	92.7±0.4	0.002
Minimum SaO_2, %	73.8±1.5	85.3±1.3	0.002
MAP, mmHg[*]	95±2	89±2	0.019
SBP, mmHg[*]	129±3	123±2	0.071
DBP, mmHg[*]	78±2	72±2	0.013
PRA, ng/L/s[†]	0.28 (0.17, 6.03)	0.24 (0.01, 4.33)	0.18
AngII, ng/L[†]	16 (12, 48)	16 (12, 73)	0.73
Aldosterone, pmol/L	179±27	115±14	0.006

[*]mean of 2 readings

[†]median (range)

AngII, angiotensin II; BMI, body mass index; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; PRA, plasma renin activity; RDI, respiratory disturbance index; SaO_2, oxyhemoglobin saturation; SBP, systolic blood pressure; UTPE, urinary total protein excretion

Table 2: Responses to Angiotensin II Infusion

Parameter	Pre-CPAP	Post-CPAP	P-value
ΔMAP, mmHg*			
15 min	10±2	15±2	0.019
30 min	11±3	14±3	0.12
45 min	17±2	21±3	0.12
60 min	16±3	17±3	0.88
90 min	4±1	3±2	0.61
ΔSBP, mmHg*			
15 min	15±4	19±4	0.18
30 min	17±5	18±4	0.37
45 min	23±4	27±5	0.077
60 min	22±4	24±5	0.67
90 min	10±3	5±3	0.33
ΔDBP, mmHg*			
15 min	7±1	13±2	0.009
30 min	8±2	12±2	0.084
45 min	14±2	17±3	0.099
60 min	13±3	14±2	0.88
90 min	1±1	2±1	0.72
ΔPRA, ng/L/s			
30 min	-0.13±0.03	-0.10±0.03	0.27
60 min	-0.23±0.08	-0.17±0.06	0.24
90 min	-0.13±0.02	-0.12±0.03	0.58
ΔAldosterone, pmol/L			
30 min	154±32	165±36	0.53
60 min	221±43	233±34	0.53
90 min	124±43	158±43	0.084

*mean of 2 readings

CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PRA, plasma renin activity; SBP, systolic blood pressure

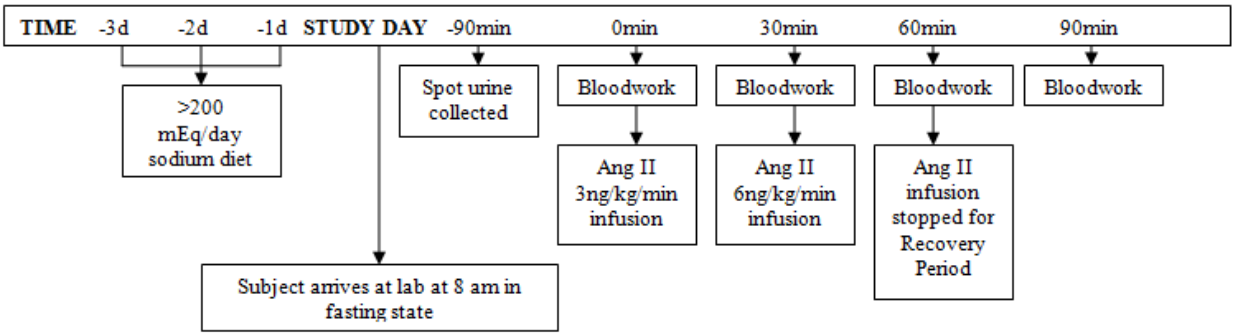

Figure 1: Study Day Protocol
AngII, angiotensin II

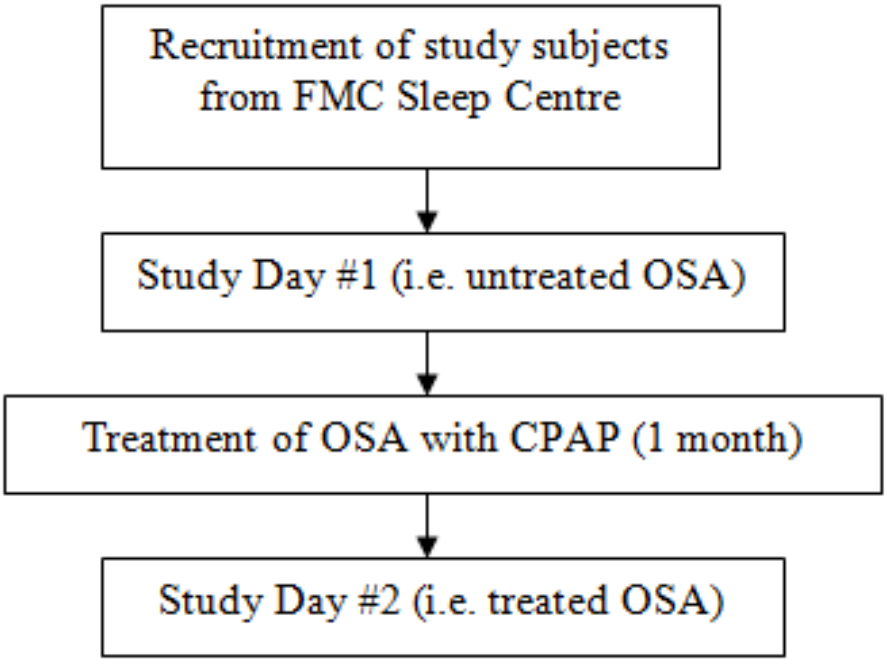

Figure 2: Overview of Study Protocol
CPAP, continuous positive airway pressure; FMC, Foothills Medical Centre; OSA, obstructive sleep apnea

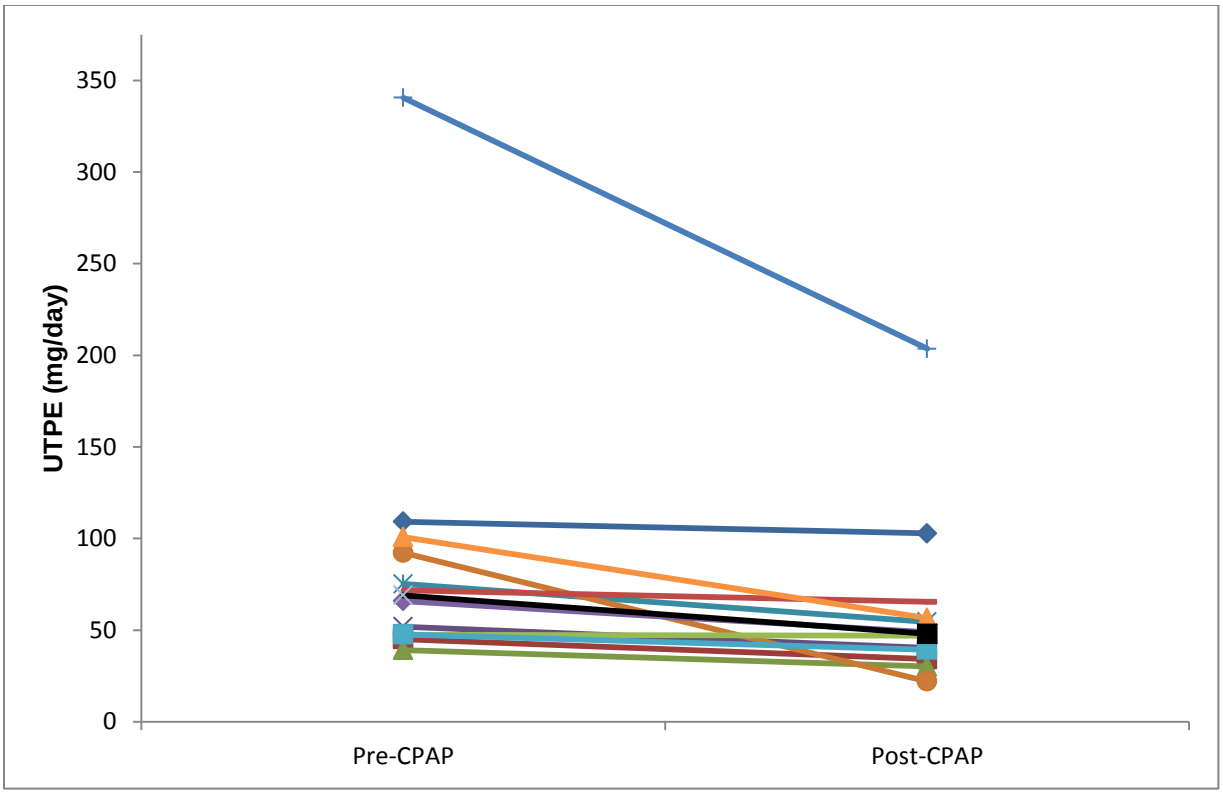

Figure 3: Urinary Total Protein Excretion pre- and post-CPAP therapy. P=0.002. CPAP, continuous positive airway pressure; UTPE, urinary total protein excretion

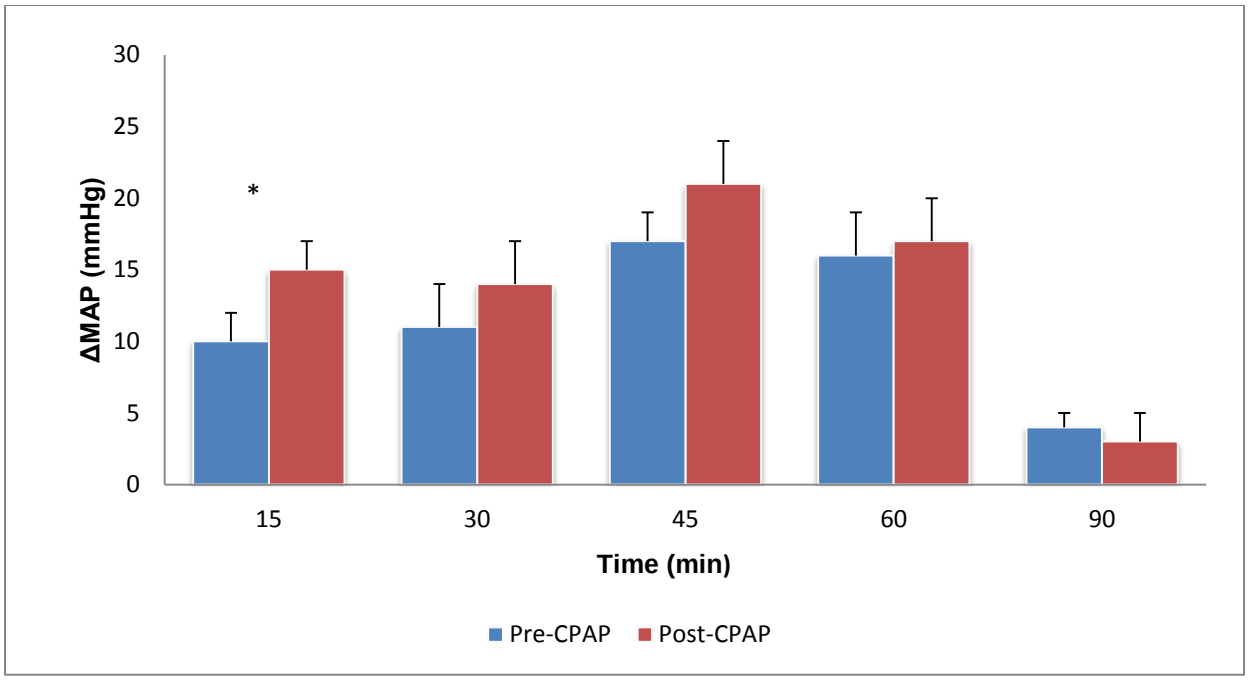

Figure 4: Mean Arterial Pressure Response to Angiotensin II Infusion pre- and post CPAP therapy. *P=0.019.
CPAP, continuous positive airway pressure; MAP, mean arterial pressure

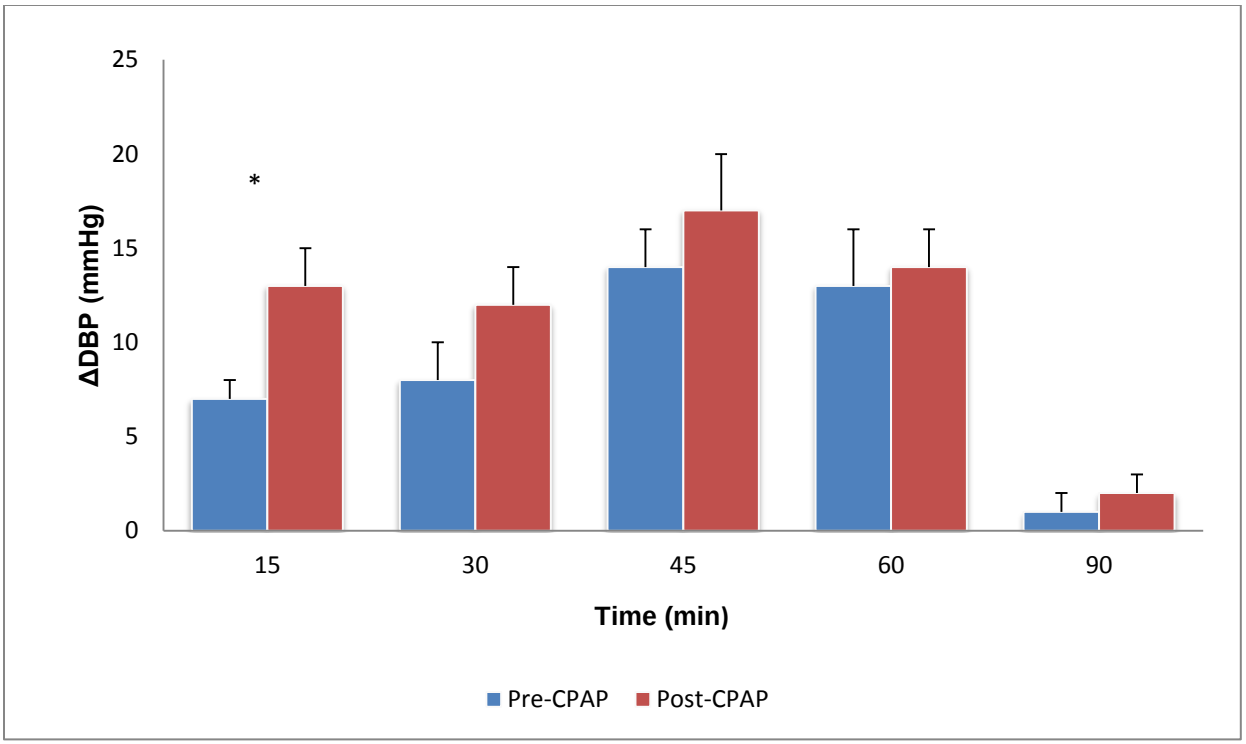

Figure 5: Diastolic Blood Pressure Response to Angiotensin II Infusion pre- and post CPAP therapy. *P=0.009.
CPAP, continuous positive airway pressure; DBP, diastolic blood pressure

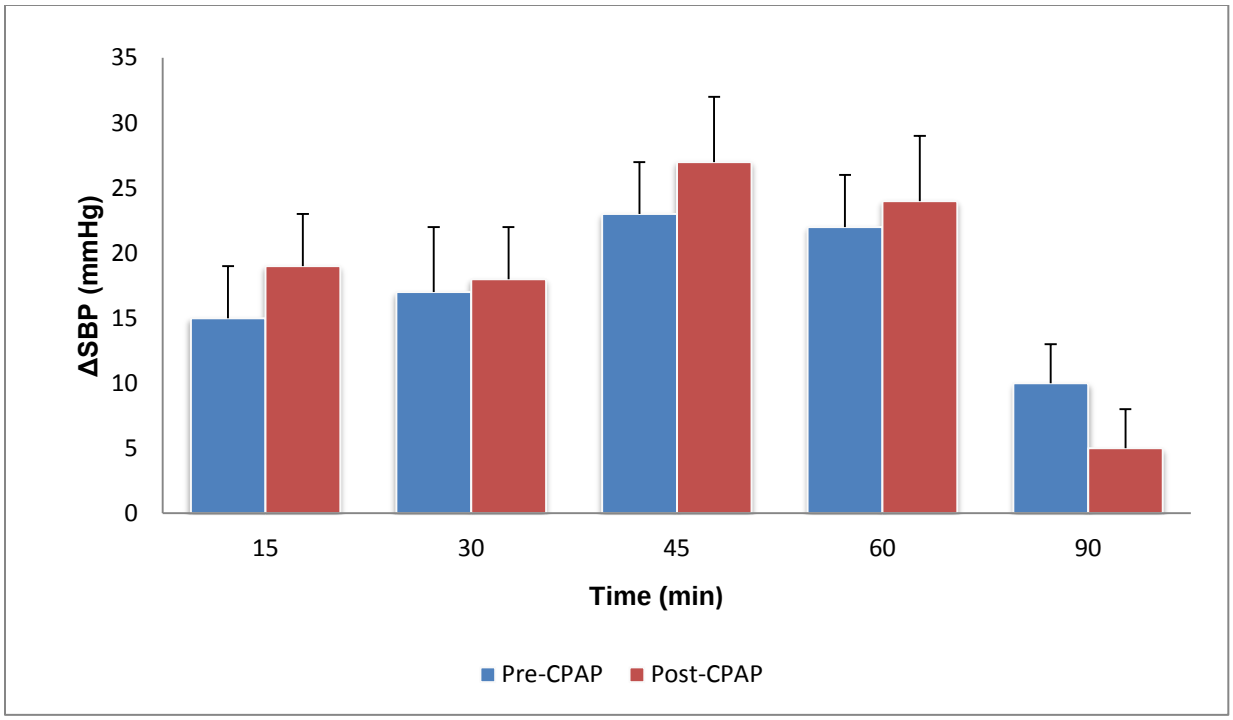

Figure 6: Systolic Blood Pressure Response to Angiotensin II Infusion pre- and post CPAP therapy. P=NS.
CPAP, continuous positive airway pressure; NS, non-significant; SBP, systolic blood pressure

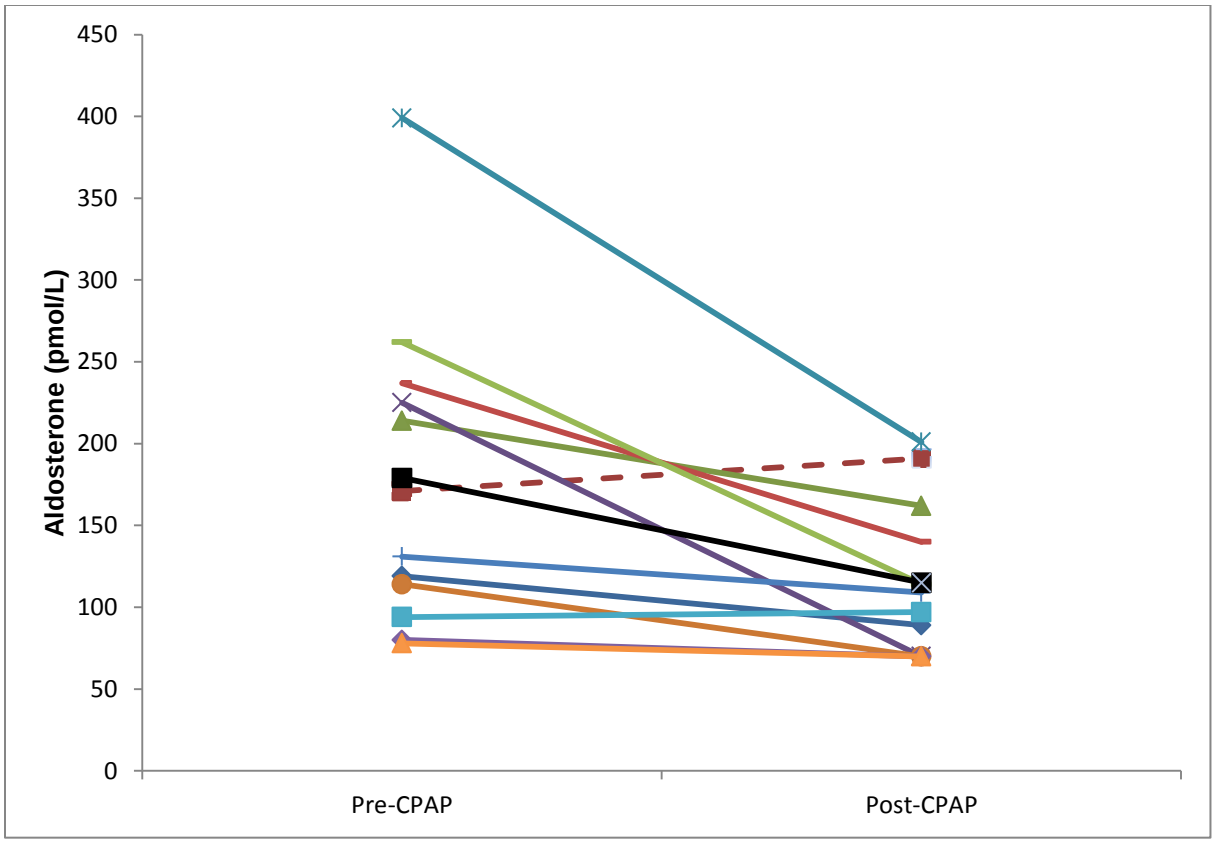

Figure 7: Aldosterone pre- and post-CPAP therapy. P=0.006.
CPAP, continuous positive airway pressure

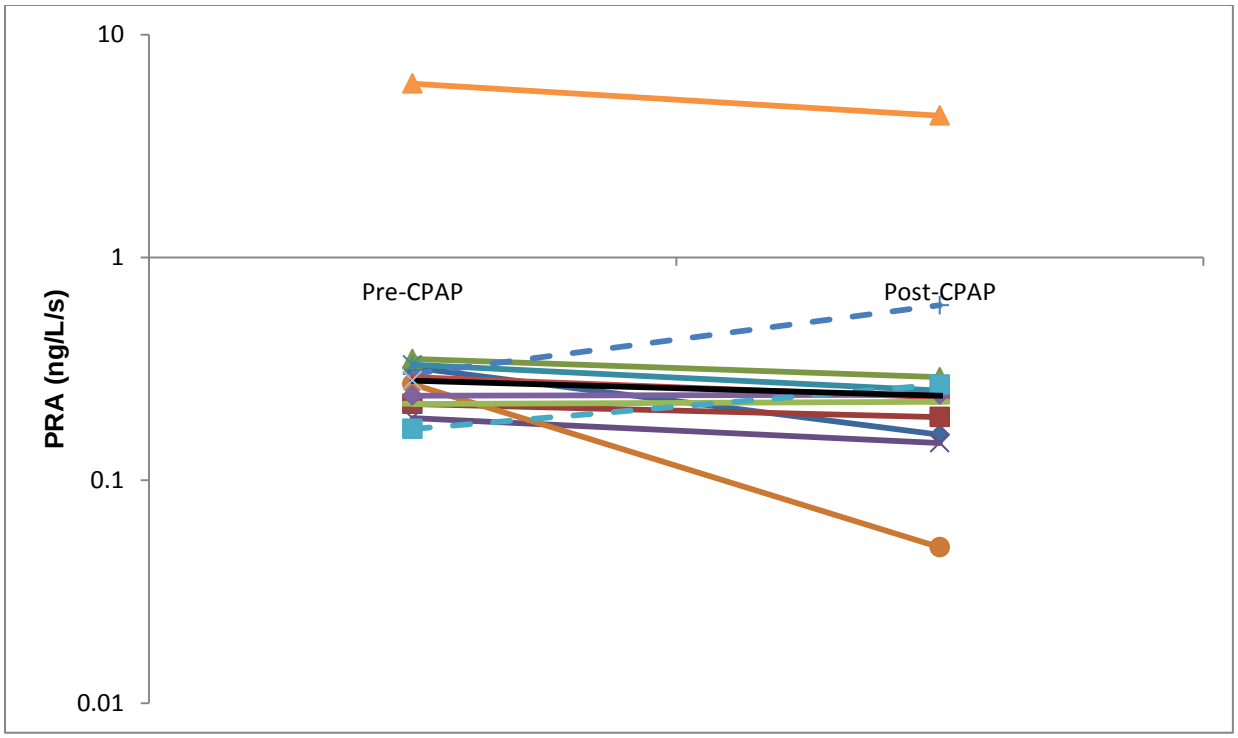

Figure 8: Plasma Renin Activity pre- and post-CPAP therapy. P=0.18.
CPAP, continuous positive airway pressure; PRA, plasma renin activity

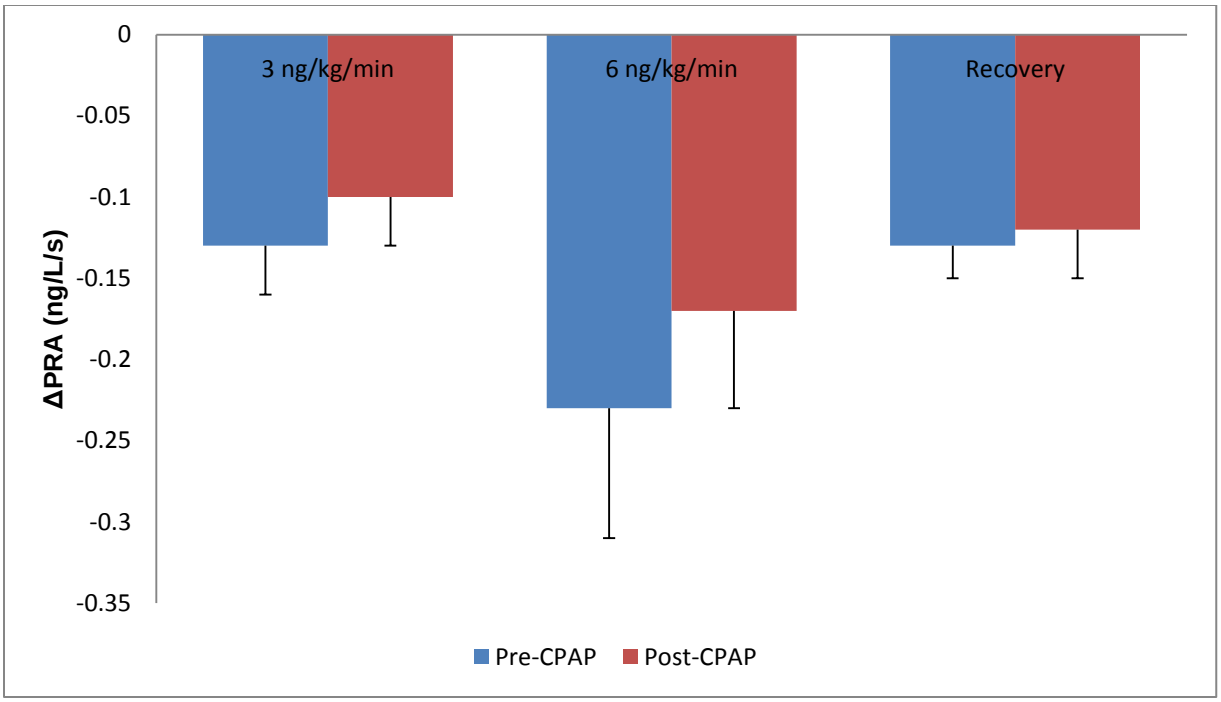

Figure 9: Plasma Renin Activity Response to Angiotensin II Infusion pre- and post CPAP therapy. P=NS.
CPAP, continuous positive airway pressure; NS, non-significant; PRA, plasma renin activity

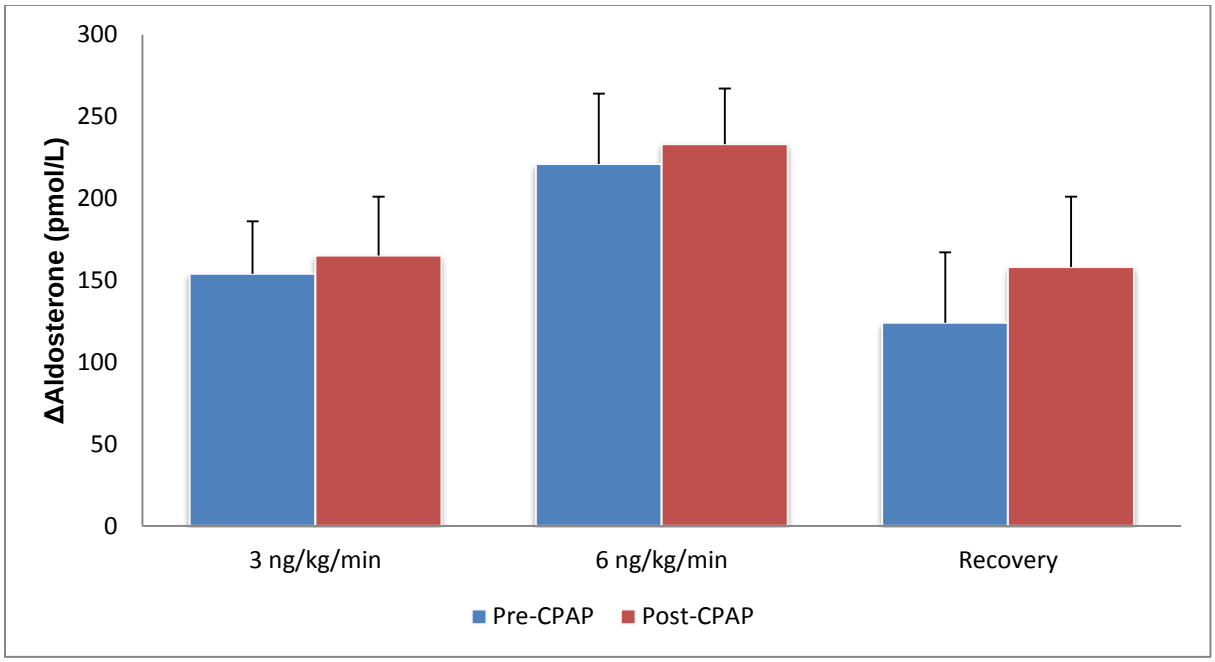

Figure 10: Aldosterone Response to Angiotensin II Infusion pre- and post CPAP therapy. P=NS.
CPAP, continuous positive airway pressure; NS, non-significant

REFERENCES

1. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G, National Kidney Foundation: National kidney foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Ann Intern Med* 139: 137-147, 2003

2. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS: Prevalence of chronic kidney disease in the united states. *JAMA* 298: 2038-2047, 2007

3. National research council canada, 2011. (accessed february 21, 2012, athttp://www.nrc-cnrc.gc.ca/eng/projects/ibd/kidney-disease.html.).

4. Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 32: S112-9, 1998

5. Foley RN, Parfrey PS, Sarnak MJ: Epidemiology of cardiovascular disease in chronic renal disease. *J Am Soc Nephrol* 9: S16-23, 1998

6. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S, RENAAL Study Investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345: 861-869, 2001

7. Levin A: Cardiac disease in chronic kidney disease: Current understandings and opportunities for change. *Blood Purif* 22: 21-27, 2004

8. Levin A, Djurdjev O, Barrett B, Burgess E, Carlisle E, Ethier J, Jindal K, Mendelssohn D, Tobe S, Singer J, Thompson C: Cardiovascular disease in patients with chronic kidney disease: Getting to the heart of the matter. *Am J Kidney Dis* 38: 1398-1407, 2001

9. Peppard PE, Young T, Palta M, Skatrud J: Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 342: 1378-1384, 2000

10. Nieto FJ, Peppard PE, Young TB: Sleep disordered breathing and metabolic syndrome. *WMJ* 108: 263-265, 2009

11. Nieto FJ, Peppard PE, Young T, Finn L, Hla KM, Farre R: Sleep disordered breathing and cancer mortality: Results from the wisconsin sleep cohort study. *Am J Respir Crit Care Med* 2012

12. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG: Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. sleep heart health study. *JAMA* 283: 1829-1836, 2000

13. Marin JM, Carrizo SJ, Vicente E, Agusti AG: Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: An observational study. *Lancet* 365: 1046-1053, 2005

14. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V: Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 353: 2034-2041, 2005

15. Botros N, Concato J, Mohsenin V, Selim B, Doctor K, Yaggi HK: Obstructive sleep apnea as a risk factor for type 2 diabetes. *Am J Med* 122: 1122-1127, 2009

16. Kono M, Tatsumi K, Saibara T, Nakamura A, Tanabe N, Takiguchi Y, Kuriyama T: Obstructive sleep apnea syndrome is associated with some components of metabolic syndrome. *Chest* 131: 1387-1392, 2007

17. Drager LF, Jun J, Polotsky VY: Obstructive sleep apnea and dyslipidemia: Implications for atherosclerosis. *Curr Opin Endocrinol Diabetes Obes* 17: 161-165, 2010

18. Drager LF, Bortolotto LA, Krieger EM, Lorenzi-Filho G: Additive effects of obstructive sleep apnea and hypertension on early markers of carotid atherosclerosis. *Hypertension* 53: 64-69, 2009

19. Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, de Paula LK, Amaro AC, Amodeo C, Bortolotto LA, Krieger EM, Bradley TD, Lorenzi-Filho G: Obstructive sleep apnea: The most common secondary cause of hypertension associated with resistant hypertension. *Hypertension* 58: 811-817, 2011

20. Drager LF, Genta PR, Pedrosa RP, Nerbass FB, Gonzaga CC, Krieger EM, Lorenzi-Filho G: Characteristics and predictors of obstructive sleep apnea in patients with systemic hypertension. *Am J Cardiol* 105: 1135-1139, 2010

21. Drager LF, Diegues-Silva L, Diniz PM, Bortolotto LA, Pedrosa RP, Couto RB, Marcondes B, Giorgi DM, Lorenzi-Filho G, Krieger EM: Obstructive sleep apnea, masked hypertension, and arterial stiffness in men. *Am J Hypertens* 23: 249-254, 2010

22. Drager LF, Pedrosa RP, Diniz PM, Diegues-Silva L, Marcondes B, Couto RB, Giorgi DM, Krieger EM, Lorenzi-Filho G: The effects of continuous positive airway pressure on prehypertension and masked hypertension in men with severe obstructive sleep apnea. *Hypertension* 57: 549-555, 2011

23. Grote L, Ploch T, Heitmann J, Knaack L, Penzel T, Peter JH: Sleep-related breathing disorder is an independent risk factor for systemic hypertension. *Am J Respir Crit Care Med* 160: 1875-1882, 1999

24. Davies CW, Crosby JH, Mullins RL, Barbour C, Davies RJ, Stradling JR: Case-control study of 24 hour ambulatory blood pressure in patients with obstructive sleep apnoea and normal matched control subjects. *Thorax* 55: 736-740, 2000

25. Goncalves SC, Martinez D, Gus M, de Abreu-Silva EO, Bertoluci C, Dutra I, Branchi T, Moreira LB, Fuchs SC, de Oliveira AC, Fuchs FD: Obstructive sleep apnea and resistant hypertension: A case-control study. *Chest* 132: 1858-1862, 2007

26. Bailey RR, Lynn KL, Burry AF, Drennan C: Proteinuria, glomerulomegaly and focal glomerulosclerosis in a grossly obese man with obstructive sleep apnea syndrome. *Aust N Z J Med* 19: 473-474, 1989

27. Chaudhary BA, Sklar AH, Chaudhary TK, Kolbeck RC, Speir WA,Jr: Sleep apnea, proteinuria, and nephrotic syndrome. *Sleep* 11: 69-74, 1988

28. Sklar AH, & Chaudhary BA: Reversible proteinuria in obstructive sleep apnea syndrome. *Arch Intern Med* 148: 87-89, 1988

29. Sklar AH, Chaudhary BA, Harp R: Nocturnal urinary protein excretion rates in patients with sleep apnea. *Nephron* 51: 35-38, 1989

30. Faulx MD, Storfer-Isser A, Kirchner HL, Jenny NS, Tracy RP, Redline S: Obstructive sleep apnea is associated with increased urinary albumin excretion. *Sleep* 30: 923-929, 2007

31. Ursavas A, Karadag M, Gullulu M, Demirdogen E, Coskun F, Onart S, Gozu RO: Low-grade urinary albumin excretion in normotensive/non-diabetic obstructive sleep apnea patients. *Sleep Breath* 12: 217-222, 2008

32. Canales MT, Paudel ML, Taylor BC, Ishani A, Mehra R, Steffes M, Stone KL, Redline S, Ensrud KE, Osteoporotic Fractures in Men (MrOS) Study Group: Sleep-disordered breathing and urinary albumin excretion in older men. *Sleep Breath* 15: 137-144, 2011

33. Krishna J, Shah ZA, Merchant M, Klein JB, Gozal D: Urinary protein expression patterns in children with sleep-disordered breathing: Preliminary findings. *Sleep Med* 7: 221-227, 2006

34. Tsioufis C, Thomopoulos C, Dimitriadis K, Amfilochiou A, Tsiachris D, Selima M, Petras D, Kallikazaros I, Stefanadis C: Association of obstructive sleep apnea with urinary albumin excretion in essential hypertension: A cross-sectional study. *Am J Kidney Dis* 52: 285-293, 2008

35. Casserly LF, Chow N, Ali S, Gottlieb DJ, Epstein LJ, Kaufman JS: Proteinuria in obstructive sleep apnea. *Kidney Int* 60: 1484-1489, 2001

36. Mello P, Franger M, Boujaoude Z, Adaimy M, Gelfand E, Kass J, Weisberg LS: Night and day proteinuria in patients with sleep apnea. *Am J Kidney Dis* 44: 636-641, 2004

37. Agrawal V, Vanhecke TE, Rai B, Franklin BA, Sangal RB, McCullough PA: Albuminuria and renal function in obese adults evaluated for obstructive sleep apnea. *Nephron Clin Pract* 113: c140-7, 2009

38. Kimmel PL, Miller G, Mendelson WB: Sleep apnea syndrome in chronic renal disease. *Am J Med* 86: 308-314, 1989

39. Markou N, Kanakaki M, Myrianthefs P, Hadjiyanakos D, Vlassopoulos D, Damianos A, Siamopoulos K, Vasiliou M, Konstantopoulos S: Sleep-disordered breathing in nondialyzed patients with chronic renal failure. *Lung* 184: 43-49, 2006

40. Canales MT, Lui LY, Taylor BC, Ishani A, Mehra R, Stone KL, Redline S, Ensrud KE, Osteoporotic Fractures in Men (MrOS) Study Group: Renal function and sleep-disordered breathing in older men. *Nephrol Dial Transplant* 23: 3908-3914, 2008

41. Sakaguchi Y, Shoji T, Kawabata H, Niihata K, Suzuki A, Kaneko T, Okada N, Isaka Y, Rakugi H, Tsubakihara Y: High prevalence of obstructive sleep apnea and its association with renal function among nondialysis chronic kidney disease patients in japan: A cross-sectional study. *Clin J Am Soc Nephrol* 6: 995-1000, 2011

42. Roumelioti ME, Buysse DJ, Sanders MH, Strollo P, Newman AB, Unruh ML: Sleep-disordered breathing and excessive daytime sleepiness in chronic kidney disease and hemodialysis. *Clin J Am Soc Nephrol* 6: 986-994, 2011

43. Nicholl DD, Ahmed SB, Loewen AH, Hemmelgarn BR, Sola DY, Beecroft JM, Turin TC, Hanly PJ: Declining kidney function increases the prevalence of sleep apnea and nocturnal hypoxia. *Chest* 141: 1422-1430, 2012

44. Sim JJ, Rasgon SA, Kujubu DA, Kumar VA, Liu IL, Shi JM, Pham TT, Derose SF: Sleep apnea in early and advanced chronic kidney disease: Kaiser permanente southern california cohort. *Chest* 135: 710-716, 2009

45. Mendelson WB, Wadhwa NK, Greenberg HE, Gujavarty K, Bergofsky E: Effects of hemodialysis on sleep apnea syndrome in end-stage renal disease. *Clin Nephrol* 33: 247-251, 1990

46. Wadhwa NK, Seliger M, Greenberg HE, Bergofsky E, Mendelson WB: Sleep related respiratory disorders in end-stage renal disease patients on peritoneal dialysis. *Perit Dial Int* 12: 51-56, 1992

47. Wadhwa NK, & Mendelson WB: A comparison of sleep-disordered respiration in ESRD patients receiving hemodialysis and peritoneal dialysis. *Adv Perit Dial* 8: 195-198, 1992

48. Stepanski E, Faber M, Zorick F, Basner R, Roth T: Sleep disorders in patients on continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol* 6: 192-197, 1995

49. Unruh ML, Sanders MH, Redline S, Piraino BM, Umans JG, Hammond TC, Sharief I, Punjabi NM, Newman AB: Sleep apnea in patients on conventional thrice-weekly hemodialysis: Comparison with matched controls from the sleep heart health study. *J Am Soc Nephrol* 17: 3503-3509, 2006

50. Hanly PJ, & Pierratos A: Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. *N Engl J Med* 344: 102-107, 2001

51. Elias RM, Castro MC, de Queiroz EL, Abensur H, Romao JE,Jr, Lorenzi-Filho G: Obstructive sleep apnea in patients on conventional and short daily hemodialysis. *Am J Nephrol* 29: 493-500, 2009

52. Ahmed SB, Ronksley PE, Hemmelgarn BR, Tsai WH, Manns BJ, Tonelli M, Klarenbach SW, Chin R, Clement FM, Hanly PJ: Nocturnal hypoxia and loss of kidney function. *PLoS One* 6: e19029, 2011

53. Hostetter TH: Prevention of the development and progression of renal disease. *J Am Soc Nephrol* 14: S144-7, 2003

54. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. the report of an american academy of sleep medicine task force. *Sleep* 22: 667-689, 1999

55. Epstein LJ, Kristo D, Strollo PJ,Jr, Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD, Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine: Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 5: 263-276, 2009

56. Horner RL: Pathophysiology of obstructive sleep apnea. *J Cardiopulm Rehabil Prev* 28: 289-298, 2008

57. Jung R, & Kuhlo W: Neurophysiological studies of abnormal night sleep and the pickwickian syndrome. *Prog Brain Res* 18: 140-159, 1965

58. Lavie P: Nothing new under the moon. historical accounts of sleep apnea syndrome. *Arch Intern Med* 144: 2025-2028, 1984

59. Flemons WW: Clinical practice. obstructive sleep apnea. *N Engl J Med* 347: 498-504, 2002

60. Issa FG, Morrison D, Hadjuk E, Iyer A, Feroah T, Remmers JE: Digital monitoring of sleep-disordered breathing using snoring sound and arterial oxygen saturation. *Am Rev Respir Dis* 148: 1023-1029, 1993

61. Vazquez JC, Tsai WH, Flemons WW, Masuda A, Brant R, Hajduk E, Whitelaw WA, Remmers JE: Automated analysis of digital oximetry in the diagnosis of obstructive sleep apnoea. *Thorax* 55: 302-307, 2000

62. Fleetham J, Ayas N, Bradley D, Fitzpatrick M, Oliver TK, Morrison D, Ryan F, Series F, Skomro R, Tsai W, Canadian Thoracic Society Sleep Disordered Breathing Committee: Canadian thoracic society 2011 guideline update: Diagnosis and treatment of sleep disordered breathing. *Can Respir J* 18: 25-47, 2011

63. Canadian Sleep Society, Blackman A, McGregor C, Dales R, Driver HS, Dumov I, Fleming J, Fraser K, George C, Khullar A, Mink J, Moffat M, Sullivan GE, Canadian Thoracic Society, Fleetham JA, Ayas N, Bradley TD, Fitzpatrick M, Kimoff J, Morrison D, Ryan F, Skomro R, Series F: Canadian sleep Society/Canadian thoracic society position paper on the use of portable monitoring for the diagnosis of obstructive sleep apnea/hypopnea in adults. *Can Respir J* 17: 229-232, 2010

64. Collop NA, Anderson WM, Boehlecke B, Claman D, Goldberg R, Gottlieb DJ, Hudgel D, Sateia M, Schwab R, Portable Monitoring Task Force of the American Academy of Sleep Medicine: Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. portable monitoring task force of the american academy of sleep medicine. *J Clin Sleep Med* 3: 737-747, 2007

65. Jennum P, & Riha RL: Epidemiology of sleep apnoea/hypopnoea syndrome and sleep-disordered breathing. *Eur Respir J* 33: 907-914, 2009

66. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S: The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 328: 1230-1235, 1993

67. Young T, Evans L, Finn L, Palta M: Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* 20: 705-706, 1997

68. Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, Walsleben JA, Finn L, Enright P, Samet JM, Sleep Heart Health Study Research Group: Predictors of sleep-disordered breathing in community-dwelling adults: The sleep heart health study. *Arch Intern Med* 162: 893-900, 2002

69. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A: Effects of age on sleep apnea in men: I. prevalence and severity. *Am J Respir Crit Care Med* 157: 144-148, 1998

70. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, Kales A: Prevalence of sleep-disordered breathing in women: Effects of gender. *Am J Respir Crit Care Med* 163: 608-613, 2001

71. Duran J, Esnaola S, Rubio R, Iztueta A: Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am J Respir Crit Care Med* 163: 685-689, 2001

72. Malhotra A, & White DP: Obstructive sleep apnoea. *Lancet* 360: 237-245, 2002

73. Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, Ancoli-Israel S, Stone KL: Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA* 306: 613-619, 2011

74. Engleman HM, Kingshott RN, Martin SE, Douglas NJ: Cognitive function in the sleep apnea/hypopnea syndrome (SAHS). *Sleep* 23 Suppl 4: S102-8, 2000

75. Engleman HM, Kingshott RN, Wraith PK, Mackay TW, Deary IJ, Douglas NJ: Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep Apnea/Hypopnea syndrome. *Am J Respir Crit Care Med* 159: 461-467, 1999

76. Kingshott RN, Vennelle M, Hoy CJ, Engleman HM, Deary IJ, Douglas NJ: Predictors of improvements in daytime function outcomes with CPAP therapy. *Am J Respir Crit Care Med* 161: 866-871, 2000

77. Bennett LS, Barbour C, Langford B, Stradling JR, Davies RJ: Health status in obstructive sleep apnea: Relationship with sleep fragmentation and daytine sleepiness, and effects of continuous positive airway pressure treatment. *Am J Respir Crit Care Med* 159: 1884-1890, 1999

78. George CF, & Smiley A: Sleep apnea & automobile crashes. *Sleep* 22: 790-795, 1999

79. George CF: Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP. *Thorax* 56: 508-512, 2001

80. Sassani A, Findley LJ, Kryger M, Goldlust E, George C, Davidson TM: Reducing motor-vehicle collisions, costs, and fatalities by treating obstructive sleep apnea syndrome. *Sleep* 27: 453-458, 2004

81. George CF: Sleep apnea, alertness, and motor vehicle crashes. *Am J Respir Crit Care Med* 176: 954-956, 2007

82. Teran-Santos J, Jimenez-Gomez A, Cordero-Guevara J: The association between sleep apnea and the risk of traffic accidents. cooperative group burgos-santander. *N Engl J Med* 340: 847-851, 1999

83. Barbe, Pericas J, Munoz A, Findley L, Anto JM, Agusti AG: Automobile accidents in patients with sleep apnea syndrome. an epidemiological and mechanistic study. *Am J Respir Crit Care Med* 158: 18-22, 1998

84. Ellen RL, Marshall SC, Palayew M, Molnar FJ, Wilson KG, Man-Son-Hing M: Systematic review of motor vehicle crash risk in persons with sleep apnea. *J Clin Sleep Med* 2: 193-200, 2006

85. Engleman HM, Hirst WS, Douglas NJ: Under reporting of sleepiness and driving impairment in patients with sleep apnoea/hypopnoea syndrome. *J Sleep Res* 6: 272-275, 1997

86. Ulfberg J, Carter N, Edling C: Sleep-disordered breathing and occupational accidents. *Scand J Work Environ Health* 26: 237-242, 2000

87. Lindberg E, Carter N, Gislason T, Janson C: Role of snoring and daytime sleepiness in occupational accidents. *Am J Respir Crit Care Med* 164: 2031-2035, 2001

88. Blankfield RP, Hudgel DW, Tapolyai AA, Zyzanski SJ: Bilateral leg edema, obesity, pulmonary hypertension, and obstructive sleep apnea. *Arch Intern Med* 160: 2357-2362, 2000

89. Blankfield RP, & Zyzanski SJ: Bilateral leg edema, pulmonary hypertension, and obstructive sleep apnea: A cross-sectional study. *J Fam Pract* 51: 561-564, 2002

90. Sforza E, Krieger J, Weitzenblum E, Apprill M, Lampert E, Ratamaharo J: Long-term effects of treatment with nasal continuous positive airway pressure on daytime lung function and pulmonary hemodynamics in patients with obstructive sleep apnea. *Am Rev Respir Dis* 141: 866-870, 1990

91. Alchanatis M, Tourkohoriti G, Kakouros S, Kosmas E, Podaras S, Jordanoglou JB: Daytime pulmonary hypertension in patients with obstructive sleep apnea: The effect of continuous positive airway pressure on pulmonary hemodynamics. *Respiration* 68: 566-572, 2001

92. Sajkov D, Wang T, Saunders NA, Bune AJ, Mcevoy RD: Continuous positive airway pressure treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 165: 152-158, 2002

93. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM, Ali T, Lebowitz M, Punjabi NM: Obstructive sleep apnea-hypopnea and incident stroke: The sleep heart health study. *Am J Respir Crit Care Med* 182: 269-277, 2010

94. Munoz R, Duran-Cantolla J, Martinez-Vila E, Gallego J, Rubio R, Aizpuru F, De La Torre G: Severe sleep apnea and risk of ischemic stroke in the elderly. *Stroke* 37: 2317-2321, 2006

95. Dyken ME, Somers VK, Yamada T, Ren ZY, Zimmerman MB: Investigating the relationship between stroke and obstructive sleep apnea. *Stroke* 27: 401-407, 1996

96. Valham F, Mooe T, Rabben T, Stenlund H, Wiklund U, Franklin KA: Increased risk of stroke in patients with coronary artery disease and sleep apnea: A 10-year follow-up. *Circulation* 118: 955-960, 2008

97. Hung J, Whitford EG, Parsons RW, Hillman DR: Association of sleep apnoea with myocardial infarction in men. *Lancet* 336: 261-264, 1990

98. Hedner J, Ejnell H, Caidahl K: Left ventricular hypertrophy independent of hypertension in patients with obstructive sleep apnoea. *J Hypertens* 8: 941-946, 1990

99. Hoffstein V, & Mateika S: Cardiac arrhythmias, snoring, and sleep apnea. *Chest* 106: 466-471, 1994

100. Shah NA, Yaggi HK, Concato J, Mohsenin V: Obstructive sleep apnea as a risk factor for coronary events or cardiovascular death. *Sleep Breath* 14: 131-136, 2010

101. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M, Shahar E: Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: The sleep heart health study. *Circulation* 122: 352-360, 2010

102. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T, American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, American Heart Association Stroke Council, American Heart Association Council on Cardiovascular Nursing, American College of Cardiology Foundation: Sleep apnea and cardiovascular disease: An american heart Association/american college of cardiology foundation scientific statement from the american heart association council for high blood pressure research professional education committee, council on clinical cardiology, stroke council, and council on cardiovascular nursing. in collaboration with the national heart, lung, and blood institute national center on sleep disorders research (national institutes of health). *Circulation* 118: 1080-1111, 2008

103. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T, Somers VK: Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol* 49: 565-571, 2007

104. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, Malouf JF, Ammash NM, Friedman PA, Somers VK: Association of atrial fibrillation and obstructive sleep apnea. *Circulation* 110: 364-367, 2004

105. Marti S, Sampol G, Munoz X, Torres F, Roca A, Lloberes P, Sagales T, Quesada P, Morell F: Mortality in severe sleep apnoea/hypopnoea syndrome patients: Impact of treatment. *Eur Respir J* 20: 1511-1518, 2002

106. Campos-Rodriguez F, Martinez-Garcia MA, de la Cruz-Moron I, Almeida-Gonzalez C, Catalan-Serra P, Montserrat JM: Cardiovascular mortality in women with obstructive sleep apnea with or without continuous positive airway pressure treatment: A cohort study. *Ann Intern Med* 156: 115-122, 2012

107. Campos-Rodriguez F, Pena-Grinan N, Reyes-Nunez N, De la Cruz-Moron I, Perez-Ronchel J, De la Vega-Gallardo F, Fernandez-Palacin A: Mortality in obstructive sleep apnea-hypopnea patients treated with positive airway pressure. *Chest* 128: 624-633, 2005

108. Lavie P, Lavie L, Herer P: All-cause mortality in males with sleep apnoea syndrome: Declining mortality rates with age. *Eur Respir J* 25: 514-520, 2005

109. Lavie P, Herer P, Lavie L: Mortality risk factors in sleep apnoea: A matched case-control study. *J Sleep Res* 16: 128-134, 2007

110. Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, Shahar E, Unruh ML, Samet JM: Sleep-

disordered breathing and mortality: A prospective cohort study. *PLoS Med* 6: e1000132, 2009

111. Marshall NS, Wong KK, Liu PY, Cullen SR, Knuiman MW, Grunstein RR: Sleep apnea as an independent risk factor for all-cause mortality: The busselton health study. *Sleep* 31: 1079-1085, 2008

112. Shpirer I, Rapoport MJ, Stav D, Elizur A: Normal and elevated HbA1C levels correlate with severity of hypoxemia in patients with obstructive sleep apnea and decrease following CPAP treatment. *Sleep Breath* 16: 461-466, 2012

113. Harsch IA, Schahin SP, Bruckner K, Radespiel-Troger M, Fuchs FS, Hahn EG, Konturek PC, Lohmann T, Ficker JH: The effect of continuous positive airway pressure treatment on insulin sensitivity in patients with obstructive sleep apnoea syndrome and type 2 diabetes. *Respiration* 71: 252-259, 2004

114. Sharma SK, Agrawal S, Damodaran D, Sreenivas V, Kadhiravan T, Lakshmy R, Jagia P, Kumar A: CPAP for the metabolic syndrome in patients with obstructive sleep apnea. *N Engl J Med* 365: 2277-2286, 2011

115. Assoumou HG, Gaspoz JM, Sforza E, Pichot V, Celle S, Maudoux D, Kossovsky M, Chouchou F, Barthelemy JC, Roche F: Obstructive sleep apnea and the metabolic syndrome in an elderly healthy population: The SYNAPSE cohort. *Sleep Breath* 2011

116. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC,Jr, Spertus JA, Costa F, American Heart Association, National Heart, Lung, and Blood Institute: Diagnosis and management of the metabolic syndrome: An american heart Association/National heart, lung, and blood institute scientific statement. *Circulation* 112: 2735-2752, 2005

117. Mickelson SA: Preoperative and postoperative management of obstructive sleep apnea patients. *Otolaryngol Clin North Am* 40: 877-889, 2007

118. Lancaster LH, Mason WR, Parnell JA, Rice TW, Loyd JE, Milstone AP, Collard HR, Malow BA: Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. *Chest* 136: 772-778, 2009

119. Fine LG, Orphanides C, Norman JT: Progressive renal disease: The chronic hypoxia hypothesis. *Kidney Int Suppl* 65: S74-8, 1998

120. Fine LG, & Norman JT: Chronic hypoxia as a mechanism of progression of chronic kidney diseases: From hypothesis to novel therapeutics. *Kidney Int* 74: 867-872, 2008

121. Kanbay A, Buyukoglan H, Ozdogan N, Kaya E, Oymak FS, Gulmez I, Demir R, Kokturk O, Covic A: Obstructive sleep apnea syndrome is related to the progression of chronic kidney disease. *Int Urol Nephrol* 44: 535-539, 2012

122. Kato K, Takata Y, Usui Y, Shiina K, Asano K, Hashimura Y, Saruhara H, Nishihata Y, Tomiyama H, Yamashina A: Severe obstructive sleep apnea increases cystatin C in clinically latent renal dysfunction. *Respir Med* 105: 643-649, 2011

123. Canales MT, Taylor BC, Ishani A, Mehra R, Steffes M, Stone KL, Redline S, Ensrud KE, Osteoporotic Fractures in Men (MrOS) Study Group: Reduced renal function and sleep-disordered breathing in community-dwelling elderly men. *Sleep Med* 9: 637-645, 2008

124. Young T, Skatrud J, Peppard PE: Risk factors for obstructive sleep apnea in adults. *JAMA* 291: 2013-2016, 2004

125. Saaresranta T, & Polo O: Sleep-disordered breathing and hormones. *Eur Respir J* 22: 161-172, 2003

126. Wetter DW, Young TB, Bidwell TR, Badr MS, Palta M: Smoking as a risk factor for sleep-disordered breathing. *Arch Intern Med* 154: 2219-2224, 1994

127. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP: Pathophysiology of sleep apnea. *Physiol Rev* 90: 47-112, 2010

128. Sanders MH, & Givelber R: Sleep disordered breathing may not be an independent risk factor for diabetes, but diabetes may contribute to the occurrence of periodic breathing in sleep. *Sleep Med* 4: 349-350, 2003

129. Buxbaum SG, Elston RC, Tishler PV, Redline S: Genetics of the apnea hypopnea index in caucasians and african americans: I. segregation analysis. *Genet Epidemiol* 22: 243-253, 2002

130. Lam B, Ip MS, Tench E, Ryan CF: Craniofacial profile in asian and white subjects with obstructive sleep apnoea. *Thorax* 60: 504-510, 2005

131. Wong ML, Sandham A, Ang PK, Wong DC, Tan WC, Huggare J: Craniofacial morphology, head posture, and nasal respiratory resistance in obstructive sleep apnoea: An inter-ethnic comparison. *Eur J Orthod* 27: 91-97, 2005

132. Haas DC, Foster GL, Nieto FJ, Redline S, Resnick HE, Robbins JA, Young T, Pickering TG: Age-dependent associations between sleep-disordered breathing and hypertension: Importance of discriminating between systolic/diastolic hypertension and isolated systolic hypertension in the sleep heart health study. *Circulation* 111: 614-621, 2005

133. Young T, Palta M, Dempsey J, Peppard PE, Nieto FJ, Hla KM: Burden of sleep apnea: Rationale, design, and major findings of the wisconsin sleep cohort study. *WMJ* 108: 246-249, 2009

134. White DP: Pathogenesis of obstructive and central sleep apnea. *Am J Respir Crit Care Med* 172: 1363-1370, 2005

135. Basner RC: Continuous positive airway pressure for obstructive sleep apnea. *N Engl J Med* 356: 1751-1758, 2007

136. Kohler M, & Stradling JR: Mechanisms of vascular damage in obstructive sleep apnea. *Nat Rev Cardiol* 7: 677-685, 2010

137. Sullivan CE, Issa FG, Berthon-Jones M, Eves L: Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet* 1: 862-865, 1981

138. Issa FG, & Sullivan CE: Reversal of central sleep apnea using nasal CPAP. *Chest* 90: 165-171, 1986

139. Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ: Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev* (3): CD001106, 2006

140. McDaid C, Duree KH, Griffin SC, Weatherly HL, Stradling JR, Davies RJ, Sculpher MJ, Westwood ME: A systematic review of continuous positive airway pressure for obstructive sleep apnoea-hypopnoea syndrome. *Sleep Med Rev* 13: 427-436, 2009

141. Patel SR, White DP, Malhotra A, Stanchina ML, Ayas NT: Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: Results of a meta-analysis. *Arch Intern Med* 163: 565-571, 2003

142. Stradling JR, & Davies RJ: Is more NCPAP better? *Sleep* 23 Suppl 4: S150-3, 2000

143. Weaver TE, Maislin G, Dinges DF, Bloxham T, George CF, Greenberg H, Kader G, Mahowald M, Younger J, Pack AI: Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep* 30: 711-719, 2007

144. Akashiba T, Minemura H, Yamamoto H, Kosaka N, Saito O, Horie T: Nasal continuous positive airway pressure changes blood pressure "non-dippers" to "dippers" in patients with obstructive sleep apnea. *Sleep* 22: 849-853, 1999

145. Becker HF, Jerrentrup A, Ploch T, Grote L, Penzel T, Sullivan CE, Peter JH: Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation* 107: 68-73, 2003

146. Coughlin SR, Mawdsley L, Mugarza JA, Wilding JP, Calverley PM: Cardiovascular and metabolic effects of CPAP in obese males with OSA. *Eur Respir J* 29: 720-727, 2007

147. Dimsdale JE, Loredo JS, Profant J: Effect of continuous positive airway pressure on blood pressure : A placebo trial. *Hypertension* 35: 144-147, 2000

148. Engleman HM, Gough K, Martin SE, Kingshott RN, Padfield PL, Douglas NJ: Ambulatory blood pressure on and off continuous positive airway pressure therapy for the sleep apnea/hypopnea syndrome: Effects in "non-dippers". *Sleep* 19: 378-381, 1996

149. Faccenda JF, Mackay TW, Boon NA, Douglas NJ: Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. *Am J Respir Crit Care Med* 163: 344-348, 2001

150. Hui DS, To KW, Ko FW, Fok JP, Chan MC, Ngai JC, Tung AH, Ho CW, Tong MW, Szeto CC, Yu CM: Nasal CPAP reduces systemic blood pressure in patients with obstructive sleep apnoea and mild sleepiness. *Thorax* 61: 1083-1090, 2006

151. Norman D, Loredo JS, Nelesen RA, Ancoli-Israel S, Mills PJ, Ziegler MG, Dimsdale JE: Effects of continuous positive airway pressure versus supplemental oxygen on 24-hour ambulatory blood pressure. *Hypertension* 47: 840-845, 2006

152. Pepin JL, Tamisier R, Barone-Rochette G, Launois SH, Levy P, Baguet JP: Comparison of continuous positive airway pressure and valsartan in hypertensive patients with sleep apnea. *Am J Respir Crit Care Med* 182: 954-960, 2010

153. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJ: Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: A randomised parallel trial. *Lancet* 359: 204-210, 2002

154. Sanner BM, Tepel M, Markmann A, Zidek W: Effect of continuous positive airway pressure therapy on 24-hour blood pressure in patients with obstructive sleep apnea syndrome. *Am J Hypertens* 15: 251-257, 2002

155. Moller DS, Lind P, Strunge B, Pedersen EB: Abnormal vasoactive hormones and 24-hour blood pressure in obstructive sleep apnea. *Am J Hypertens* 16: 274-280, 2003

156. Barbe F, Duran-Cantolla J, Capote F, de la Pena M, Chiner E, Masa JF, Gonzalez M, Marin JM, Garcia-Rio F, de Atauri JD, Teran J, Mayos M, Monasterio C, del Campo F, Gomez S, de la Torre MS, Martinez M, Montserrat JM, Spanish Sleep and Breathing Group: Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. *Am J Respir Crit Care Med* 181: 718-726, 2010

157. Peker Y, Hedner J, Johansson A, Bende M: Reduced hospitalization with cardiovascular and pulmonary disease in obstructive sleep apnea patients on nasal CPAP treatment. *Sleep* 20: 645-653, 1997

158. Buchner NJ, Sanner BM, Borgel J, Rump LC: Continuous positive airway pressure treatment of mild to moderate obstructive sleep apnea reduces cardiovascular risk. *Am J Respir Crit Care Med* 176: 1274-1280, 2007

159. He J, Kryger MH, Zorick FJ, Conway W, Roth T: Mortality and apnea index in obstructive sleep apnea. experience in 385 male patients. *Chest* 94: 9-14, 1988

160. Partinen M, Jamieson A, Guilleminault C: Long-term outcome for obstructive sleep apnea syndrome patients. mortality. *Chest* 94: 1200-1204, 1988

161. Zimmerman ME, Arnedt JT, Stanchina M, Millman RP, Aloia MS: Normalization of memory performance and positive airway pressure adherence in memory-impaired patients with obstructive sleep apnea. *Chest* 130: 1772-1778, 2006

162. Mar J, Rueda JR, Duran-Cantolla J, Schechter C, Chilcott J: The cost-effectiveness of nCPAP treatment in patients with moderate-to-severe obstructive sleep apnoea. *Eur Respir J* 21: 515-522, 2003

163. Albarrak M, Banno K, Sabbagh AA, Delaive K, Walld R, Manfreda J, Kryger MH: Utilization of healthcare resources in obstructive sleep apnea syndrome: A 5-year follow-up study in men using CPAP. *Sleep* 28: 1306-1311, 2005

164. McDaid C, Griffin S, Weatherly H, Duree K, van der Burgt M, van Hout S, Akers J, Davies RJ, Sculpher M, Westwood M: Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea-hypopnoea syndrome: A systematic review and economic analysis. *Health Technol Assess* 13: iii-iv, xi-xiv, 1-119, 143-274, 2009

165. Tan MC, Ayas NT, Mulgrew A, Cortes L, FitzGerald JM, Fleetham JA, Schulzer M, Ryan CF, Ghaeli R, Cooper P, Marra CA: Cost-effectiveness of continuous positive airway pressure therapy in patients with obstructive sleep apnea-hypopnea in british columbia. *Can Respir J* 15: 159-165, 2008

166. Gurubhagavatula I, Nkwuo JE, Maislin G, Pack AI: Estimated cost of crashes in commercial drivers supports screening and treatment of obstructive sleep apnea. *Accid Anal Prev* 40: 104-115, 2008

167. Schulz R, Mahmoudi S, Hattar K, Sibelius U, Olschewski H, Mayer K, Seeger W, Grimminger F: Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea. impact of continuous positive airway pressure therapy. *Am J Respir Crit Care Med* 162: 566-570, 2000

168. Jelic S, Padeletti M, Kawut SM, Higgins C, Canfield SM, Onat D, Colombo PC, Basner RC, Factor P, LeJemtel TH: Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. *Circulation* 117: 2270-2278, 2008

169. Alonso-Fernandez A, Garcia-Rio F, Arias MA, Hernanz A, de la Pena M, Pierola J, Barcelo A, Lopez-Collazo E, Agusti A: Effects of CPAP on oxidative stress and nitrate efficiency in sleep apnoea: A randomised trial. *Thorax* 64: 581-586, 2009

170. Jelic S, Lederer DJ, Adams T, Padeletti M, Colombo PC, Factor PH, Le Jemtel TH: Vascular inflammation in obesity and sleep apnea. *Circulation* 121: 1014-1021, 2010

171. Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G, Hirano T, Adachi M: Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. *Circulation* 107: 1129-1134, 2003

172. Drager LF, Bortolotto LA, Figueiredo AC, Krieger EM, Lorenzi GF: Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med* 176: 706-712, 2007

173. Phillips CL, Yang Q, Williams A, Roth M, Yee BJ, Hedner JA, Berend N, Grunstein RR: The effect of short-term withdrawal from continuous positive airway pressure therapy on sympathetic activity and markers of vascular inflammation in subjects with obstructive sleep apnoea. *J Sleep Res* 16: 217-225, 2007

174. Phillips BG, Narkiewicz K, Pesek CA, Haynes WG, Dyken ME, Somers VK: Effects of obstructive sleep apnea on endothelin-1 and blood pressure. *J Hypertens* 17: 61-66, 1999

175. Narkiewicz K, Kato M, Phillips BG, Pesek CA, Davison DE, Somers VK: Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea. *Circulation* 100: 2332-2335, 1999

176. Kohler M, Pepperell JC, Casadei B, Craig S, Crosthwaite N, Stradling JR, Davies RJ: CPAP and measures of cardiovascular risk in males with OSAS. *Eur Respir J* 32: 1488-1496, 2008

177. Ziegler MG, Mills PJ, Loredo JS, Ancoli-Israel S, Dimsdale JE: Effect of continuous positive airway pressure and placebo treatment on sympathetic nervous activity in patients with obstructive sleep apnea. *Chest* 120: 887-893, 2001

178. Noda A, Nakata S, Koike Y, Miyata S, Kitaichi K, Nishizawa T, Nagata K, Yasuma F, Murohara T, Yokota M: Continuous positive airway pressure improves daytime baroreflex sensitivity and nitric oxide production in patients with moderate to severe obstructive sleep apnea syndrome. *Hypertens Res* 30: 669-676, 2007

179. Ip MS, Tse HF, Lam B, Tsang KW, Lam WK: Endothelial function in obstructive sleep apnea and response to treatment. *Am J Respir Crit Care Med* 169: 348-353, 2004

180. Cross MD, Mills NL, Al-Abri M, Riha R, Vennelle M, Mackay TW, Newby DE, Douglas NJ: Continuous positive airway pressure improves vascular function in obstructive sleep apnoea/hypopnoea syndrome: A randomised controlled trial. *Thorax* 63: 578-583, 2008

181. Gay P, Weaver T, Loube D, Iber C, Positive Airway Pressure Task Force, Standards of Practice Committee, American Academy of Sleep Medicine: Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. *Sleep* 29: 381-401, 2006

182. Kribbs NB, Pack AI, Kline LR, Getsy JE, Schuett JS, Henry JN, Maislin G, Dinges DF: Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. *Am Rev Respir Dis* 147: 1162-1168, 1993

183. Kohler M, Stoewhas AC, Ayers L, Senn O, Bloch KE, Russi EW, Stradling JR: Effects of continuous positive airway pressure therapy withdrawal in patients with obstructive sleep apnea: A randomized controlled trial. *Am J Respir Crit Care Med* 184: 1192-1199, 2011

184. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF,3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration): A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150: 604-612, 2009

185. U S renal data system, USRDS 2011 annual data report: Atlas of chronic kidney disease and end-stage renal disease in the united states, national institutes of health, national institute of diabetes and digestive and kidney diseases, bethesda, MD, 2011.

186. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296-1305, 2004

187. Menon V, Wang X, Sarnak MJ, Hunsicker LH, Madero M, Beck GJ, Collins AJ, Kusek JW, Levey AS, Greene T: Long-term outcomes in nondiabetic chronic kidney disease. *Kidney Int* 73: 1310-1315, 2008

188. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH: Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 164: 659-663, 2004

189. Swaminathan S, & Shah SV: Novel inflammatory mechanisms of accelerated atherosclerosis in kidney disease. *Kidney Int* 80: 453-463, 2011

190. Abboud H, & Henrich WL: Clinical practice. stage IV chronic kidney disease. *N Engl J Med* 362: 56-65, 2010

191. Foster MC, Hwang SJ, Larson MG, Parikh NI, Meigs JB, Vasan RS, Wang TJ, Levy D, Fox CS: Cross-classification of microalbuminuria and reduced glomerular filtration rate: Associations between cardiovascular disease risk factors and clinical outcomes. *Arch Intern Med* 167: 1386-1392, 2007

192. Arnlov J, Evans JC, Meigs JB, Wang TJ, Fox CS, Levy D, Benjamin EJ, D'Agostino RB, Vasan RS: Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: The framingham heart study. *Circulation* 112: 969-975, 2005

193. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S, HOPE Study Investigators: Albuminuria and risk

of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 286: 421-426, 2001

194. Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlof B, Devereux RB, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wan Y: Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: Losartan intervention for endpoint reduction in hypertension study. *Hypertension* 45: 198-202, 2005

195. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H, Appleyard M, Jensen JS: Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation* 110: 32-35, 2004

196. Wachtell K, Ibsen H, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlof B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristianson K, Lederballe-Pedersen O, Nieminen MS, Okin PM, Omvik P, Oparil S, Wedel H, Snapinn SM, Aurup P: Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: The LIFE study. *Ann Intern Med* 139: 901-906, 2003

197. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, de Jong PE, Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group: Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 106: 1777-1782, 2002

198. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, Wiebe N, Tonelli M, Alberta Kidney Disease Network: Relation between kidney function, proteinuria, and adverse outcomes. *JAMA* 303: 423-429, 2010

199. Tonelli M, Muntner P, Lloyd A, Manns BJ, James MT, Klarenbach S, Quinn RR, Wiebe N, Hemmelgarn BR, Alberta Kidney Disease Network: Using proteinuria and estimated glomerular filtration rate to classify risk in patients with chronic kidney disease: A cohort study. *Ann Intern Med* 154: 12-21, 2011

200. Wang TJ, Evans JC, Meigs JB, Rifai N, Fox CS, D'Agostino RB, Levy D, Vasan RS: Low-grade albuminuria and the risks of hypertension and blood pressure progression. *Circulation* 111: 1370-1376, 2005

201. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Cooper ME, Mitch WE, Brenner BM: Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation* 110: 921-927, 2004

202. Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P: N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA* 293: 1609-1616, 2005

203. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. the heart outcomes prevention evaluation study investigators. *N Engl J Med* 342: 145-153, 2000

204. Lewis EF, Solomon SD, Jablonski KA, Rice MM, Clemenza F, Hsia J, Maggioni AP, Zabalgoitia M, Huynh T, Cuddy TE, Gersh BJ, Rouleau J, Braunwald E, Pfeffer MA, PEACE Investigators: Predictors of heart failure in patients with stable coronary artery disease: A PEACE study. *Circ Heart Fail* 2: 209-216, 2009

205. Ruggenenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G: Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. "gruppo italiano di studi epidemiologici in nefrologia" (GISEN). *Kidney Int* 53: 1209-1216, 1998

206. Keane WF, Brenner BM, de Zeeuw D, Grunfeld JP, McGill J, Mitch WE, Ribeiro AB, Shahinfar S, Simpson RL, Snapinn SM, Toto R, RENAAL Study Investigators: The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: The RENAAL study. *Kidney Int* 63: 1499-1507, 2003

207. Romundstad S, Holmen J, Kvenild K, Hallan H, Ellekjaer H: Microalbuminuria and all-cause mortality in 2,089 apparently healthy individuals: A 4.4-year follow-up study. the nord-trondelag health study (HUNT), norway. *Am J Kidney Dis* 42: 466-473, 2003

208. Davies DF, & Shock NW: Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J Clin Invest* 29: 496-507, 1950

209. Hemmelgarn BR, Zhang J, Manns BJ, Tonelli M, Larsen E, Ghali WA, Southern DA, McLaughlin K, Mortis G, Culleton BF: Progression of kidney dysfunction in the community-dwelling elderly. *Kidney Int* 69: 2155-2161, 2006

210. Fuiano G, Sund S, Mazza G, Rosa M, Caglioti A, Gallo G, Natale G, Andreucci M, Memoli B, De Nicola L, Conte G: Renal hemodynamic response to maximal vasodilating stimulus in healthy older subjects. *Kidney Int* 59: 1052-1058, 2001

211. Iseki K, Iseki C, Ikemiya Y, Fukiyama K: Risk of developing end-stage renal disease in a cohort of mass screening. *Kidney Int* 49: 800-805, 1996

212. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS: Body mass index and risk for end-stage renal disease. *Ann Intern Med* 144: 21-28, 2006

213. Serra A, Romero R, Lopez D, Navarro M, Esteve A, Perez N, Alastrue A, Ariza A: Renal injury in the extremely obese patients with normal renal function. *Kidney Int* 73: 947-955, 2008

214. Pinto-Sietsma SJ, Mulder J, Janssen WM, Hillege HL, de Zeeuw D, de Jong PE: Smoking is related to albuminuria and abnormal renal function in nondiabetic persons. *Ann Intern Med* 133: 585-591, 2000

215. Bleyer AJ, Shemanski LR, Burke GL, Hansen KJ, Appel RG: Tobacco, hypertension, and vascular disease: Risk factors for renal functional decline in an older population. *Kidney Int* 57: 2072-2079, 2000

216. Orth SR, Schroeder T, Ritz E, Ferrari P: Effects of smoking on renal function in patients with type 1 and type 2 diabetes mellitus. *Nephrol Dial Transplant* 20: 2414-2419, 2005

217. Parving HH, Lewis JB, Ravid M, Remuzzi G, Hunsicker LG, DEMAND investigators: Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: A global perspective. *Kidney Int* 69: 2057-2063, 2006

218. Warmoth L, Regalado MM, Simoni J, Harrist RB, Wesson DE: Cigarette smoking enhances increased urine albumin excretion as a risk factor for glomerular filtration rate decline in primary hypertension. *Am J Med Sci* 330: 111-119, 2005

219. Lin SJ, Koford JK, Baird BC, Hurdle JF, Krikov S, Habib AN, Goldfarb-Rumyantzev AS: Effect of donors' intravenous drug use, cigarette smoking, and alcohol dependence on kidney transplant outcome. *Transplantation* 80: 482-486, 2005

220. Sun F, Tao Q, Zhan S: Metabolic syndrome and the development of chronic kidney disease among 118 924 non-diabetic taiwanese in a retrospective cohort. *Nephrology (Carlton)* 15: 84-92, 2010

221. Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V, Whelton PK, He J: The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann Intern Med* 140: 167-174, 2004

222. Kurella M, Lo JC, Chertow GM: Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol* 16: 2134-2140, 2005

223. Schaeffner ES, Kurth T, Curhan GC, Glynn RJ, Rexrode KM, Baigent C, Buring JE, Gaziano JM: Cholesterol and the risk of renal dysfunction in apparently healthy men. *J Am Soc Nephrol* 14: 2084-2091, 2003

224. Cusick M, Chew EY, Hoogwerf B, Agron E, Wu L, Lindley A, Ferris FL,3rd, Early Treatment Diabetic Retinopathy Study Research Group: Risk factors for renal replacement therapy in the early treatment diabetic retinopathy study (ETDRS), early treatment diabetic retinopathy study report no. 26. *Kidney Int* 66: 1173-1179, 2004

225. Perry HM,Jr, Miller JP, Fornoff JR, Baty JD, Sambhi MP, Rutan G, Moskowitz DW, Carmody SE: Early predictors of 15-year end-stage renal disease in hypertensive patients. *Hypertension* 25: 587-594, 1995

226. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB, Stamler J: Blood pressure and end-stage renal disease in men. *N Engl J Med* 334: 13-18, 1996

227. Garg AX, Clark WF, Haynes RB, House AA: Moderate renal insufficiency and the risk of cardiovascular mortality: Results from the NHANES I. *Kidney Int* 61: 1486-1494, 2002

228. Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, Salem DN, Levey AS, Sarnak MJ: Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: A pooled analysis of community-based studies. *J Am Soc Nephrol* 15: 1307-1315, 2004

229. Iseki K, Tohyama K, Matsumoto T, Nakamura H: High prevalence of chronic kidney disease among patients with sleep related breathing disorder (SRBD). *Hypertens Res* 31: 249-255, 2008

230. Fleischmann G, Fillafer G, Matterer H, Skrabal F, Kotanko P: Prevalence of chronic kidney disease in patients with suspected sleep apnoea. *Nephrol Dial Transplant* 25: 181-186, 2010

231. Chou YT, Lee PH, Yang CT, Lin CL, Veasey S, Chuang LP, Lin SW, Lin YS, Chen NH: Obstructive sleep apnea: A stand-alone risk factor for chronic kidney disease. *Nephrol Dial Transplant* 26: 2244-2250, 2011

232. Sim JJ, Rasgon SA, Derose SF: Sleep apnea and hypertension: Prevalence in chronic kidney disease. *J Clin Hypertens (Greenwich)* 9: 837-841, 2007

233. Masuda T, Murata M, Honma S, Iwazu Y, Sasaki N, Ogura M, Onishi A, Ando Y, Muto S, Shimada K, Kario K, Kusano E, Asano Y: Sleep-disordered breathing predicts cardiovascular events and mortality in hemodialysis patients. *Nephrol Dial Transplant* 26: 2289-2295, 2011

234. Tang SC, Lam B, Yao TJ, Leung WS, Chu CM, Ho YW, Ip MS, Lai KN: Sleep apnea is a novel risk predictor of cardiovascular morbidity and death in patients receiving peritoneal dialysis. *Kidney Int* 77: 1031-1038, 2010

235. Jung HH, Lee JH, Baek HJ, Kim SJ, Lee JJ: Nocturnal hypoxemia and periodic limb movement predict mortality in patients on maintenance hemodialysis. *Clin J Am Soc Nephrol* 5: 1607-1613, 2010

236. Pressman MR, Benz RL, Schleifer CR, Peterson DD: Sleep disordered breathing in ESRD: Acute beneficial effects of treatment with nasal continuous positive airway pressure. *Kidney Int* 43: 1134-1139, 1993

237. Jurado-Gamez B, Martin-Malo A, Alvarez-Lara MA, Munoz L, Cosano A, Aljama P: Sleep disorders are underdiagnosed in patients on maintenance hemodialysis. *Nephron Clin Pract* 105: c35-42, 2007

238. Beecroft JM, Pierratos A, Hanly PJ: Clinical presentation of obstructive sleep apnea in patients with end-stage renal disease. *J Clin Sleep Med* 5: 115-121, 2009

239. Nicholl DD, Ahmed SB, Loewen AH, Hemmelgarn BR, Sola DY, Beecroft JM, Turin TC, Hanly PJ: Clinical presentation of obstructive sleep apnea in patients with chronic kidney disease. *J Clin Sleep Med* 2012 (In Press)

240. Tada T, Kusano KF, Ogawa A, Iwasaki J, Sakuragi S, Kusano I, Takatsu S, Miyazaki M, Ohe T: The predictors of central and obstructive sleep apnoea in haemodialysis patients. *Nephrol Dial Transplant* 22: 1190-1197, 2007

241. de Oliveira Rodrigues CJ, Marson O, Tufic S, Kohlmann O,Jr, Guimaraes SM, Togeiro P, Ribeiro AB, Tavares A: Relationship among end-stage renal disease, hypertension, and sleep apnea in nondiabetic dialysis patients. *Am J Hypertens* 18: 152-157, 2005

242. Beecroft J, Duffin J, Pierratos A, Chan CT, McFarlane P, Hanly PJ: Enhanced chemo-responsiveness in patients with sleep apnoea and end-stage renal disease. *Eur Respir J* 28: 151-158, 2006

243. Beecroft JM, Zaltzman J, Prasad R, Meliton G, Hanly PJ: Impact of kidney transplantation on sleep apnoea in patients with end-stage renal disease. *Nephrol Dial Transplant* 22: 3028-3033, 2007

244. Jean G, Piperno D, Francois B, Charra B: Sleep apnea incidence in maintenance hemodialysis patients: Influence of dialysate buffer. *Nephron* 71: 138-142, 1995

245. Tang SC, Lam B, Ku PP, Leung WS, Chu CM, Ho YW, Ip MS, Lai KN: Alleviation of sleep apnea in patients with chronic renal failure by nocturnal cycler-assisted peritoneal dialysis compared with conventional continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol* 17: 2607-2616, 2006

246. Jurado-Gamez B, Martin-Malo A, Rodriguez-Benot A, Munoz-Cabrera L, Cosano Povedano A, Aljama P: Kidney transplantation improves sleep-related breathing in hemodialysis patients. *Blood Purif* 26: 485-490, 2008

247. Auckley DH, Schmidt-Nowara W, Brown LK: Reversal of sleep apnea hypopnea syndrome in end-stage renal disease after kidney transplantation. *Am J Kidney Dis* 34: 739-744, 1999

248. Langevin B, Fouque D, Leger P, Robert D: Sleep apnea syndrome and end-stage renal disease. cure after renal transplantation. *Chest* 103: 1330-1335, 1993

249. Lee JJ, Kim GS, Kim JA, Kim SJ, Kang JG, Kim GH, Jung HH: Improvement of sleep-related breathing disorder in patients with end-stage renal disease after kidney transplantation. *Clin Transplant* 25: 126-130, 2011

250. Rodrigues CJ, Marson O, Togeiro SM, Tufik S, Ribeiro AB, Tavares A: Sleep-disordered breathing changes after kidney transplantation: A polysomnographic study. *Nephrol Dial Transplant* 25: 2011-2015, 2010

251. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP: Using the berlin questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 131: 485-491, 1999

252. Molnar MZ, Szentkiralyi A, Lindner A, Czira ME, Szabo A, Mucsi I, Novak M: High prevalence of patients with a high risk for obstructive sleep apnoea syndrome after kidney transplantation--association with declining renal function. *Nephrol Dial Transplant* 22: 2686-2692, 2007

253. Szentkiralyi A, Czira ME, Molnar MZ, Kovesdy CP, Remport A, Szeifert L, Vamos EP, Juhasz J, Turanyi CZ, Mucsi I, Novak M: High risk of obstructive sleep apnea is a risk factor of death censored graft loss in kidney transplant recipients: An observational cohort study. *Sleep Med* 12: 267-273, 2011

254. Nicholl DD, Ahmed SB, Loewen AH, Hemmelgarn BR, Sola DY, Beecroft JM, Turin TC, Hanly PJ: Diagnostic accuracy of screening instruments for identifying obstructive sleep apnea in kidney failure. *J Clin Sleep Med* 2012 (In Press)

255. Younes M, Ostrowski M, Thompson W, Leslie C, Shewchuk W: Chemical control stability in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 163: 1181-1190, 2001

256. Beecroft JM, Duffin J, Pierratos A, Chan CT, McFarlane P, Hanly PJ: Decreased chemosensitivity and improvement of sleep apnea by nocturnal hemodialysis. *Sleep Med* 10: 47-54, 2009

257. Banerjee D, Ma JZ, Collins AJ, Herzog CA: Long-term survival of incident hemodialysis patients who are hospitalized for congestive heart failure, pulmonary edema, or fluid overload. *Clin J Am Soc Nephrol* 2: 1186-1190, 2007

258. Arneson TJ, Liu J, Qiu Y, Gilbertson DT, Foley RN, Collins AJ: Hospital treatment for fluid overload in the medicare hemodialysis population. *Clin J Am Soc Nephrol* 5: 1054-1063, 2010

259. Caravaca F, Martinez del Viejo C, Villa J, Martinez Gallardo R, Ferreira F: Hydration status assessment by multi-frequency bioimpedance in patients with advanced chronic kidney disease. *Nefrologia* 31: 537-544, 2011

260. Wizemann V, Wabel P, Chamney P, Zaluska W, Moissl U, Rode C, Malecka-Masalska T, Marcelli D: The mortality risk of overhydration in haemodialysis patients. *Nephrol Dial Transplant* 24: 1574-1579, 2009

261. Anastassov GE, & Trieger N: Edema in the upper airway in patients with obstructive sleep apnea syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 86: 644-647, 1998

262. Elias RM, Bradley TD, Kasai T, Motwani SS, Chan CT: Rostral overnight fluid shift in end-stage renal disease: Relationship with obstructive sleep apnea. *Nephrol Dial Transplant* 27: 1569-1573, 2012

263. Beecroft JM, Hoffstein V, Pierratos A, Chan CT, McFarlane PA, Hanly PJ: Pharyngeal narrowing in end-stage renal disease: Implications for obstructive sleep apnoea. *Eur Respir J* 30: 965-971, 2007

264. Beecroft JM, Hoffstein V, Pierratos A, Chan CT, McFarlane P, Hanly PJ: Nocturnal haemodialysis increases pharyngeal size in patients with sleep apnoea and end-stage renal disease. *Nephrol Dial Transplant* 23: 673-679, 2008

265. Tang SC, Lam B, Lai AS, Pang CB, Tso WK, Khong PL, Ip MS, Lai KN: Improvement in sleep apnea during nocturnal peritoneal dialysis is associated with reduced airway congestion and better uremic clearance. *Clin J Am Soc Nephrol* 4: 410-418, 2009

266. Chiu KL, Ryan CM, Shiota S, Ruttanaumpawan P, Arzt M, Haight JS, Chan CT, Floras JS, Bradley TD: Fluid shift by lower body positive pressure increases pharyngeal resistance in healthy subjects. *Am J Respir Crit Care Med* 174: 1378-1383, 2006

267. Shiota S, Ryan CM, Chiu KL, Ruttanaumpawan P, Haight J, Arzt M, Floras JS, Chan C, Bradley TD: Alterations in upper airway cross-sectional area in response to lower body positive pressure in healthy subjects. *Thorax* 62: 868-872, 2007

268. Redolfi S, Yumino D, Ruttanaumpawan P, Yau B, Su MC, Lam J, Bradley TD: Relationship between overnight rostral fluid shift and obstructive sleep apnea in nonobese men. *Am J Respir Crit Care Med* 179: 241-246, 2009

269. Yumino D, Redolfi S, Ruttanaumpawan P, Su MC, Smith S, Newton GE, Mak S, Bradley TD: Nocturnal rostral fluid shift: A unifying concept for the pathogenesis of obstructive and central sleep apnea in men with heart failure. *Circulation* 121: 1598-1605, 2010

270. Redolfi S, Arnulf I, Pottier M, Lajou J, Koskas I, Bradley TD, Similowski T: Attenuation of obstructive sleep apnea by compression stockings in subjects with venous insufficiency. *Am J Respir Crit Care Med* 184: 1062-1066, 2011

271. Redolfi S, Arnulf I, Pottier M, Bradley TD, Similowski T: Effects of venous compression of the legs on overnight rostral fluid shift and obstructive sleep apnea. *Respir Physiol Neurobiol* 175: 390-393, 2011

272. Su MC, Chiu KL, Ruttanaumpawan P, Shiota S, Yumino D, Redolfi S, Haight JS, Yau B, Lam J, Bradley TD: Difference in upper airway collapsibility during wakefulness between men and women in response to lower-body positive pressure. *Clin Sci (Lond)* 116: 713-720, 2009

273. Kasai T, Motwani SS, Yumino D, Mak S, Newton GE, Bradley TD: Differing relationship of nocturnal fluid shifts to sleep apnea in men and women with heart failure. *Circ Heart Fail* 2012

274. Pimenta E, Calhoun DA, Oparil S: Sleep apnea, aldosterone, and resistant hypertension. *Prog Cardiovasc Dis* 51: 371-380, 2009

275. Pratt-Ubunama MN, Nishizaka MK, Boedefeld RL, Cofield SS, Harding SM, Calhoun DA: Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. *Chest* 131: 453-459, 2007

276. Gonzaga CC, Gaddam KK, Ahmed MI, Pimenta E, Thomas SJ, Harding SM, Oparil S, Cofield SS, Calhoun DA: Severity of obstructive sleep apnea is related to aldosterone status in subjects with resistant hypertension. *J Clin Sleep Med* 6: 363-368, 2010

277. Gaddam K, Pimenta E, Thomas SJ, Cofield SS, Oparil S, Harding SM, Calhoun DA: Spironolactone reduces severity of obstructive sleep apnoea in patients with resistant hypertension: A preliminary report. *J Hum Hypertens* 24: 532-537, 2010

278. Boyd JH, Petrof BJ, Hamid Q, Fraser R, Kimoff RJ: Upper airway muscle inflammation and denervation changes in obstructive sleep apnea. *Am J Respir Crit Care Med* 170: 541-546, 2004

279. Kimoff RJ, Sforza E, Champagne V, Ofiara L, Gendron D: Upper airway sensation in snoring and obstructive sleep apnea. *Am J Respir Crit Care Med* 164: 250-255, 2001

280. Jennette JC, Charles L, Grubb W: Glomerulomegaly and focal segmental glomerulosclerosis associated with obesity and sleep-apnea syndrome. *Am J Kidney Dis* 10: 470-472, 1987

281. Haase VH: Pathophysiological consequences of HIF activation: HIF as a modulator of fibrosis. *Ann N Y Acad Sci* 1177: 57-65, 2009

282. Zoccali C, Benedetto FA, Tripepi G, Cambareri F, Panuccio V, Candela V, Mallamaci F, Enia G, Labate C, Tassone F: Nocturnal hypoxemia, night-day arterial pressure changes and left ventricular geometry in dialysis patients. *Kidney Int* 53: 1078-1084, 1998

283. Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Candela V, Labate C, Tassone F: Left ventricular hypertrophy and nocturnal hypoxemia in hemodialysis patients. *J Hypertens* 19: 287-293, 2001

284. Fletcher EC, Lesske J, Behm R, Miller CC,3rd, Stauss H, Unger T: Carotid chemoreceptors, systemic blood pressure, and chronic episodic hypoxia mimicking sleep apnea. *J Appl Physiol* 72: 1978-1984, 1992

285. Fletcher EC, Lesske J, Qian W, Miller CC,3rd, Unger T: Repetitive, episodic hypoxia causes diurnal elevation of blood pressure in rats. *Hypertension* 19: 555-561, 1992

286. Zoccali C, Mallamaci F, Tripepi G: Traditional and emerging cardiovascular risk factors in end-stage renal disease. *Kidney Int Suppl* (85): S105-10, 2003

287. Zoccali C, Mallamaci F, Tripepi G: Sleep apnea in renal patients. *J Am Soc Nephrol* 12: 2854-2859, 2001

288. Erten Y, Kokturk O, Yuksel A, Elbeg S, Ciftci TU, Pasaoglu H, Ozkan S, Bali M, Arinsoi T, Sindel S: Relationship between sleep complaints and proinflammatory cytokines in haemodialysis patients. *Nephrology (Carlton)* 10: 330-335, 2005

289. Koehnlein T, Schmidt A, Moesenthin M, Dierkes J, Neumann KH, Welte T: Increased cardiac troponin T and C-reactive protein levels in end-stage renal disease are associated with obstructive sleep apnea. *Clin Nephrol* 71: 50-58, 2009

290. Fletcher EC, Lesske J, Culman J, Miller CC, Unger T: Sympathetic denervation blocks blood pressure elevation in episodic hypoxia. *Hypertension* 20: 612-619, 1992

291. Lesske J, Fletcher EC, Bao G, Unger T: Hypertension caused by chronic intermittent hypoxia--influence of chemoreceptors and sympathetic nervous system. *J Hypertens* 15: 1593-1603, 1997

292. Bao G, Metreveli N, Li R, Taylor A, Fletcher EC: Blood pressure response to chronic episodic hypoxia: Role of the sympathetic nervous system. *J Appl Physiol* 83: 95-101, 1997

293. Zoccali C, Mallamaci F, Tripepi G, Benedetto FA: Autonomic neuropathy is linked to nocturnal hypoxaemia and to concentric hypertrophy and remodelling in dialysis patients. *Nephrol Dial Transplant* 16: 70-77, 2001

294. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM: Hyperfiltration in remnant nephrons: A potentially adverse response to renal ablation. *J Am Soc Nephrol* 12: 1315-1325, 2001

295. Brenner BM, Meyer TW, Hostetter TH: Dietary protein intake and the progressive nature of kidney disease: The role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N Engl J Med* 307: 652-659, 1982

296. Kinebuchi S, Kazama JJ, Satoh M, Sakai K, Nakayama H, Yoshizawa H, Narita I, Suzuki E, Gejyo F: Short-term use of continuous positive airway pressure ameliorates glomerular hyperfiltration in patients with obstructive sleep apnoea syndrome. *Clin Sci (Lond)* 107: 317-322, 2004

297. Williams B, Baker AQ, Gallacher B, Lodwick D: Angiotensin II increases vascular permeability factor gene expression by human vascular smooth muscle cells. *Hypertension* 25: 913-917, 1995

298. Fletcher EC, Bao G, Miller CC,3rd: Effect of recurrent episodic hypocapnic, eucapnic, and hypercapnic hypoxia on systemic blood pressure. *J Appl Physiol* 78: 1516-1521, 1995

299. Fletcher EC: An animal model of the relationship between systemic hypertension and repetitive episodic hypoxia as seen in sleep apnoea. *J Sleep Res* 4: 71-77, 1995

300. Fletcher EC, & Bao G: The rat as a model of chronic recurrent episodic hypoxia and effect upon systemic blood pressure. *Sleep* 19: S210-2, 1996

301. Fletcher EC, Bao G, Li R: Renin activity and blood pressure in response to chronic episodic hypoxia. *Hypertension* 34: 309-314, 1999

302. Fletcher EC, Orolinova N, Bader M: Blood pressure response to chronic episodic hypoxia: The renin-angiotensin system. *J Appl Physiol* 92: 627-633, 2002

303. Foster GE, Hanly PJ, Ahmed SB, Beaudin AE, Pialoux V, Poulin MJ: Intermittent hypoxia increases arterial blood pressure in humans through a renin-angiotensin system-dependent mechanism. *Hypertension* 56: 369-377, 2010

304. Patel SR, Larkin EK, Mignot E, Lin L, Redline S: The association of angiotensin converting enzyme (ACE) polymorphisms with sleep apnea and hypertension. *Sleep* 30: 531-533, 2007

305. Bostrom KB, Hedner J, Melander O, Grote L, Gullberg B, Rastam L, Groop L, Lindblad U: Interaction between the angiotensin-converting enzyme gene insertion/deletion polymorphism and obstructive sleep apnoea as a mechanism for hypertension. *J Hypertens* 25: 779-783, 2007

306. Kraiczi H, Hedner J, Peker Y, Carlson J: Increased vasoconstrictor sensitivity in obstructive sleep apnea. *J Appl Physiol* 89: 493-498, 2000

307. Svatikova A, Olson LJ, Wolk R, Phillips BG, Adachi T, Schwartz GL, Somers VK: Obstructive sleep apnea and aldosterone. *Sleep* 32: 1589-1592, 2009

308. Di Murro A, Petramala L, Cotesta D, Zinnamosca L, Crescenzi E, Marinelli C, Saponara M, Letizia C: Renin-angiotensin-aldosterone system in patients with sleep apnoea: Prevalence of primary aldosteronism. *J Renin Angiotensin Aldosterone Syst* 11: 165-172, 2010

309. Nicholl DDM, Hanly P, Handley G, Hemmelgarn B, Poulin M, Sola D, Ahmed SB: Obstructive sleep apnea and the vascular renin angiotensin system in humans. *American Journal of Respiratory and Critical Care Medicine* 185: A2185, 2012

310. Ahmed SB, Kang AK, Burns KD, Kennedy CR, Lai V, Cattran DC, Scholey JW, Miller JA: Effects of oral contraceptive use on the renal and systemic vascular response to angiotensin II infusion. *J Am Soc Nephrol* 15: 780-786, 2004

311. Ahmed SB, Hovind P, Parving HH, Rossing P, Price DA, Laffel LM, Lansang MC, Stevanovic R, Fisher ND, Hollenberg NK: Oral contraceptives, angiotensin-dependent renal vasoconstriction, and risk of diabetic nephropathy. *Diabetes Care* 28: 1988-1994, 2005

312. Ahmed SB, Fisher ND, Stevanovic R, Hollenberg NK: Body mass index and angiotensin-dependent control of the renal circulation in healthy humans. *Hypertension* 46: 1316-1320, 2005

313. Nicholl DD, Hemmelgarn BR, Turin TC, MacRae JM, Muruve DA, Sola DY, Ahmed SB: Increased urinary protein excretion in the "normal" range is associated with increased renin-angiotensin system activity. *Am J Physiol Renal Physiol* 302: F526-32, 2012

314. Mann MC, Exner DV, Hemmelgarn BR, Turin TC, Sola DY, Ahmed SB: Impact of gender on the cardiac autonomic response to angiotensin II in healthy humans. *J Appl Physiol* 2012

315. Price DA, Fisher ND, Osei SY, Lansang MC, Hollenberg NK: Renal perfusion and function in healthy african americans. *Kidney Int* 59: 1037-1043, 2001

316. Price DA, Fisher ND, Lansang MC, Stevanovic R, Williams GH, Hollenberg NK: Renal perfusion in blacks: Alterations caused by insuppressibility of intrarenal renin with salt. *Hypertension* 40: 186-189, 2002

317. Miller JA, Anacta LA, Cattran DC: Impact of gender on the renal response to angiotensin II. *Kidney Int* 55: 278-285, 1999

318. Miller JA, Cherney DZ, Duncan JA, Lai V, Burns KD, Kennedy CR, Zimpelmann J, Gao W, Cattran DC, Scholey JW: Gender differences in the renal response to renin-angiotensin system blockade. *J Am Soc Nephrol* 17: 2554-2560, 2006

319. Page A, Reich H, Zhou J, Lai V, Cattran DC, Scholey JW, Miller JA: Endothelial nitric oxide synthase gene/gender interactions and the renal hemodynamic response to angiotensin II. *J Am Soc Nephrol* 16: 3053-3060, 2005

320. Cherney DZ, Scholey JW, Nasrallah R, Dekker MG, Slorach C, Bradley TJ, Hebert RL, Sochett EB, Miller JA: Renal hemodynamic effect of cyclooxygenase 2 inhibition in young men and women with uncomplicated type 1 diabetes mellitus. *Am J Physiol Renal Physiol* 294: F1336-41, 2008

321. Cherney DZ, Miller JA, Scholey JW, Bradley TJ, Slorach C, Curtis JR, Dekker MG, Nasrallah R, Hebert RL, Sochett EB: The effect of cyclooxygenase-2 inhibition on renal hemodynamic function in humans with type 1 diabetes. *Diabetes* 57: 688-695, 2008

322. Conlin PR, Seely EW, Hollenberg NK, Williams GH: Dissociation of vascular and adrenal responsiveness to angiotensin II following calcium channel blockade. *Endocr Res* 24: 127-139, 1998

323. Seely EW, Brosnihan KB, Jeunemaitre X, Okamura K, Williams GH, Hollenberg NK, Herrington DM: Effects of conjugated oestrogen and droloxifene on the renin-angiotensin system, blood pressure and renal blood flow in postmenopausal women. *Clin Endocrinol (Oxf)* 60: 315-321, 2004

324. Forman JP, Williams JS, Fisher ND: Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. *Hypertension* 55: 1283-1288, 2010

325. Vaidya A, Forman JP, Williams JS: Vitamin D and the vascular sensitivity to angiotensin II in obese caucasians with hypertension. *J Hum Hypertens* 2010

326. Shoback DM, Williams GH, Swartz SL, Davies RO, Hollenberg NK: Time course and effect of sodium intake on vascular and hormonal responses to enalapril (MK 421) in normal subjects. *J Cardiovasc Pharmacol* 5: 1010-1018, 1983

327. Kawasaki T, Itoh K, Uezono K, Sasaki H: A simple method for estimating 24 h urinary sodium and potassium excretion from second morning voiding urine specimen in adults. *Clin Exp Pharmacol Physiol* 20: 7-14, 1993

328. Bosma RJ, Kwakernaak AJ, van der Heide JJ, de Jong PE, Navis GJ: Body mass index and glomerular hyperfiltration in renal transplant recipients: Cross-sectional analysis and long-term impact. *Am J Transplant* 7: 645-652, 2007

329. Vander AJ, Wilde WS, Malvin RL, Sullivan LP: Re-examination of salt and water retention in congestive heart failure: Significance of renal filtration fraction. *Am J Med* 25: 497-502, 1958

330. Follenius M, Krieger J, Krauth MO, Sforza F, Brandenberger G: Obstructive sleep apnea treatment: Peripheral and central effects on plasma renin activity and aldosterone. *Sleep* 14: 211-217, 1991

331. Saarelainen S, Hasan J, Siitonen S, Seppala E: Effect of nasal CPAP treatment on plasma volume, aldosterone and 24-h blood pressure in obstructive sleep apnoea. *J Sleep Res* 5: 181-185, 1996

332. Meston N, Davies RJ, Mullins R, Jenkinson C, Wass JA, Stradling JR: Endocrine effects of nasal continuous positive airway pressure in male patients with obstructive sleep apnoea. *J Intern Med* 254: 447-454, 2003

333. Barbe F, Mayoralas LR, Duran J, Masa JF, Maimo A, Montserrat JM, Monasterio C, Bosch M, Ladaria A, Rubio M, Rubio R, Medinas M, Hernandez L, Vidal S, Douglas NJ, Agusti AG: Treatment with continuous positive airway pressure is not effective in patients with

sleep apnea but no daytime sleepiness. a randomized, controlled trial. *Ann Intern Med* 134: 1015-1023, 2001

334. Barnes M, Houston D, Worsnop CJ, Neill AM, Mykytyn IJ, Kay A, Trinder J, Saunders NA, Douglas McEvoy R, Pierce RJ: A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. *Am J Respir Crit Care Med* 165: 773-780, 2002

335. Campos-Rodriguez F, Grilo-Reina A, Perez-Ronchel J, Merino-Sanchez M, Gonzalez-Benitez MA, Beltran-Robles M, Almeida-Gonzalez C: Effect of continuous positive airway pressure on ambulatory BP in patients with sleep apnea and hypertension: A placebo-controlled trial. *Chest* 129: 1459-1467, 2006

336. Robinson GV, Smith DM, Langford BA, Davies RJ, Stradling JR: Continuous positive airway pressure does not reduce blood pressure in nonsleepy hypertensive OSA patients. *Eur Respir J* 27: 1229-1235, 2006

337. Alajmi M, Mulgrew AT, Fox J, Davidson W, Schulzer M, Mak E, Ryan CF, Fleetham J, Choi P, Ayas NT: Impact of continuous positive airway pressure therapy on blood pressure in patients with obstructive sleep apnea hypopnea: A meta-analysis of randomized controlled trials. *Lung* 185: 67-72, 2007

338. Bazzano LA, Khan Z, Reynolds K, He J: Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. *Hypertension* 50: 417-423, 2007

339. Haentjens P, Van Meerhaeghe A, Moscariello A, De Weerdt S, Poppe K, Dupont A, Velkeniers B: The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome: Evidence from a meta-analysis of placebo-controlled randomized trials. *Arch Intern Med* 167: 757-764, 2007

340. Folkow B: The haemodynamic consequences of adaptive structural changes of the resistance vessels in hypertension. *Clin Sci* 41: 1-12, 1971

341. Langille BL: Remodeling of developing and mature arteries: Endothelium, smooth muscle, and matrix. *J Cardiovasc Pharmacol* 21 Suppl 1: S11-7, 1993

342. Shepard JW,Jr: Gas exchange and hemodynamics during sleep. *Med Clin North Am* 69: 1243-1264, 1985

343. Fletcher EC, Miller J, Schaaf JW, Fletcher JG: Urinary catecholamines before and after tracheostomy in patients with obstructive sleep apnea and hypertension. *Sleep* 10: 35-44, 1987

344. Krieger J, Benzoni D, Sforza E, Sassard J: Urinary excretion of prostanoids during sleep in obstructive sleep apnoea patients. *Clin Exp Pharmacol Physiol* 18: 551-555, 1991

345. Saarelainen S, Seppala E, Laasonen K, Hasan J: Circulating endothelin-1 in obstructive sleep apnea. *Endothelium* 5: 115-118, 1997

346. Daemen MJ, Lombardi DM, Bosman FT, Schwartz SM: Angiotensin II induces smooth muscle cell proliferation in the normal and injured rat arterial wall. *Circ Res* 68: 450-456, 1991

347. Ahmed SB, Kang AK, Burns KD, Kennedy CR, Lai V, Cattran DC, Scholey JW, Miller JA: Effects of oral contraceptive use on the renal and systemic vascular response to angiotensin II infusion. *J Am Soc Nephrol* 15: 780-786, 2004

348. Clemson B, Gaul L, Gubin SS, Campsey DM, McConville J, Nussberger J, Zelis R: Prejunctional angiotensin II receptors. facilitation of norepinephrine release in the human forearm. *J Clin Invest* 93: 684-691, 1994

349. Dijkhorst-Oei LT, Stroes ES, Koomans HA, Rabelink TJ: Acute simultaneous stimulation of nitric oxide and oxygen radicals by angiotensin II in humans in vivo. *J Cardiovasc Pharmacol* 33: 420-424, 1999

350. Cline WH,Jr: Role of released catecholamines in the vascular response to injected angiotensin II in the dog. *J Pharmacol Exp Ther* 216: 104-110, 1981

351. Taddei S, Favilla S, Duranti P, Simonini N, Salvetti A: Vascular renin-angiotensin system and neurotransmission in hypertensive persons. *Hypertension* 18: 266-277, 1991

352. Carlson JT, Hedner J, Elam M, Ejnell H, Sellgren J, Wallin BG: Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. *Chest* 103: 1763-1768, 1993

353. Hedner J, Ejnell H, Sellgren J, Hedner T, Wallin G: Is high and fluctuating muscle nerve sympathetic activity in the sleep apnoea syndrome of pathogenetic importance for the development of hypertension? *J Hypertens Suppl* 6: S529-31, 1988

354. Cherney DZ, Scholey JW, Cattran DC, Kang AK, Zimpelmann J, Kennedy C, Lai V, Burns KD, Miller JA: The effect of oral contraceptives on the nitric oxide system and renal function. *Am J Physiol Renal Physiol* 293: F1539-44, 2007

355. Hein L, Barsh GS, Pratt RE, Dzau VJ, Kobilka BK: Behavioural and cardiovascular effects of disrupting the angiotensin II type-2 receptor in mice. *Nature* 377: 744-747, 1995

356. Seyedi N, Xu X, Nasjletti A, Hintze TH: Coronary kinin generation mediates nitric oxide release after angiotensin receptor stimulation. *Hypertension* 26: 164-170, 1995

357. Gohlke P, Pees C, Unger T: AT2 receptor stimulation increases aortic cyclic GMP in SHRSP by a kinin-dependent mechanism. *Hypertension* 31: 349-355, 1998

358. Pees C, Unger T, Gohlke P: Effect of angiotensin AT2 receptor stimulation on vascular cyclic GMP production in normotensive wistar kyoto rats. *Int J Biochem Cell Biol* 35: 963-972, 2003

359. Arima S, Endo Y, Yaoita H, Omata K, Ogawa S, Tsunoda K, Abe M, Takeuchi K, Abe K, Ito S: Possible role of P-450 metabolite of arachidonic acid in vasodilator mechanism of angiotensin II type 2 receptor in the isolated microperfused rabbit afferent arteriole. *J Clin Invest* 100: 2816-2823, 1997

360. Cortelli P, Parchi P, Sforza E, Contin M, Pierangeli G, Barletta G, Lugaresi E: Cardiovascular autonomic dysfunction in normotensive awake subjects with obstructive sleep apnoea syndrome. *Clin Auton Res* 4: 57-62, 1994

361. Kijima K, Matsubara H, Murasawa S, Maruyama K, Ohkubo N, Mori Y, Inada M: Regulation of angiotensin II type 2 receptor gene by the protein kinase C-calcium pathway. *Hypertension* 27: 529-534, 1996

362. Drexler H, Hayoz D, Munzel T, Hornig B, Just H, Brunner HR, Zelis R: Endothelial function in chronic congestive heart failure. *Am J Cardiol* 69: 1596-1601, 1992

363. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. the GISEN group (gruppo italiano di studi epidemiologici in nefrologia). *Lancet* 349: 1857-1863, 1997

364. Apperloo AJ, de Zeeuw D, de Jong PE: Short-term antiproteinuric response to antihypertensive treatment predicts long-term GFR decline in patients with non-diabetic renal disease. *Kidney Int Suppl* 45: S174-8, 1994

365. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Cooper ME, Mitch WE, Brenner BM: Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: Lessons from RENAAL. *Kidney Int* 65: 2309-2320, 2004

366. Ruggenenti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, Brusegan V, Rubis N, Gherardi G, Arnoldi F, Ganeva M, Ene-Iordache B, Gaspari F, Perna A, Bossi A, Trevisan R, Dodesini AR, Remuzzi G, Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators: Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 351: 1941-1951, 2004

367. Calvo G, & de Andres-Trelles F: Albuminuria as a surrogate marker for drug development: A european regulatory perspective. *Kidney Int Suppl* (92): S126-7, 2004

368. Van de Wal RM, Voors AA, Gansevoort RT: Urinary albumin excretion and the renin-angiotensin system in cardiovascular risk management. *Expert Opin Pharmacother* 7: 2505-2520, 2006

369. Jensen JS, Borch-Johnsen K, Jensen G, Feldt-Rasmussen B: Microalbuminuria reflects a generalized transvascular albumin leakiness in clinically healthy subjects. *Clin Sci (Lond)* 88: 629-633, 1995

370. Festa A, D'Agostino R, Howard G, Mykkanen L, Tracy RP, Haffner SM: Inflammation and microalbuminuria in nondiabetic and type 2 diabetic subjects: The insulin resistance atherosclerosis study. *Kidney Int* 58: 1703-1710, 2000

371. Clausen P, Jensen JS, Jensen G, Borch-Johnsen K, Feldt-Rasmussen B: Elevated urinary albumin excretion is associated with impaired arterial dilatory capacity in clinically healthy subjects. *Circulation* 103: 1869-1874, 2001

372. Schieffer B, Schieffer E, Hilfiker-Kleiner D, Hilfiker A, Kovanen PT, Kaartinen M, Nussberger J, Harringer W, Drexler H: Expression of angiotensin II and interleukin 6 in human coronary atherosclerotic plaques: Potential implications for inflammation and plaque instability. *Circulation* 101: 1372-1378, 2000

373. Warnholtz A, Nickenig G, Schulz E, Macharzina R, Brasen JH, Skatchkov M, Heitzer T, Stasch JP, Griendling KK, Harrison DG, Bohm M, Meinertz T, Munzel T: Increased NADH-oxidase-mediated superoxide production in the early stages of atherosclerosis: Evidence for involvement of the renin-angiotensin system. *Circulation* 99: 2027-2033, 1999

374. Gomez-Garre D, Largo R, Tejera N, Fortes J, Manzarbeitia F, Egido J: Activation of NF-kappaB in tubular epithelial cells of rats with intense proteinuria: Role of angiotensin II and endothelin-1. *Hypertension* 37: 1171-1178, 2001

375. Mathers CD, Sadana R, Salomon JA, Murray CJ, Lopez AD: Healthy life expectancy in 191 countries, 1999. *Lancet* 357: 1685-1691, 2001

376. Davies RJ, Crosby J, Prothero A, Stradling JR: Ambulatory blood pressure and left ventricular hypertrophy in subjects with untreated obstructive sleep apnoea and snoring, compared with matched control subjects, and their response to treatment. *Clin Sci (Lond)* 86: 417-424, 1994

377. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration: Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 360: 1903-1913, 2002

378. Kannel WB: Elevated systolic blood pressure as a cardiovascular risk factor. *Am J Cardiol* 85: 251-255, 2000

379. Staessen JA, Gasowski J, Wang JG, Thijs L, Den Hond E, Boissel JP, Coope J, Ekbom T, Gueyffier F, Liu L, Kerlikowske K, Pocock S, Fagard RH: Risks of untreated and treated isolated systolic hypertension in the elderly: Meta-analysis of outcome trials. *Lancet* 355: 865-872, 2000

380. Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, Levy D: Does the relation of blood pressure to coronary heart disease risk change with aging? the framingham heart study. *Circulation* 103: 1245-1249, 2001

381. Neal B, MacMahon S, Chapman N, Blood Pressure Lowering Treatment Trialists' Collaboration: Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: Results of prospectively designed overviews of randomised trials. blood pressure lowering treatment trialists' collaboration. *Lancet* 356: 1955-1964, 2000

382. Hebert PR, Moser M, Mayer J, Glynn RJ, Hennekens CH: Recent evidence on drug therapy of mild to moderate hypertension and decreased risk of coronary heart disease. *Arch Intern Med* 153: 578-581, 1993

383. Ogden LG, He J, Lydick E, Whelton PK: Long-term absolute benefit of lowering blood pressure in hypertensive patients according to the JNC VI risk stratification. *Hypertension* 35: 539-543, 2000

384. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators: Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 348: 1309-1321, 2003

385. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. randomized aldactone evaluation study investigators. *N Engl J Med* 341: 709-717, 1999

386. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B, EMPHASIS-HF Study Group: Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 364: 11-21, 2011

387. Rossi E, Regolisti G, Negro A, Sani C, Davoli S, Perazzoli F: High prevalence of primary aldosteronism using postcaptopril plasma aldosterone to renin ratio as a screening test among italian hypertensives. *Am J Hypertens* 15: 896-902, 2002

388. Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, Weissmann P: Hyperaldosteronism among black and white subjects with resistant hypertension. *Hypertension* 40: 892-896, 2002

389. Daskalopoulou SS, Khan NA, Quinn RR, Ruzicka M, McKay DW, Hackam DG, Rabkin SW, Rabi DM, Gilbert RE, Padwal RS, Dawes M, Touyz RM, Campbell TS, Cloutier L, Grover S, Honos G, Herman RJ, Schiffrin EL, Bolli P, Wilson T, Feldman RD, Lindsay MP, Hemmelgarn BR, Hill MD, Gelfer M, Burns KD, Vallee M, Prasad GV, Lebel M, McLean D, Arnold JM, Moe GW, Howlett JG, Boulanger JM, Larochelle P, Leiter LA, Jones C, Ogilvie RI, Woo V, Kaczorowski J, Trudeau L, Bacon SL, Petrella RJ, Milot A, Stone JA, Drouin D, Lamarre-Cliche M, Godwin M, Tremblay G, Hamet P, Fodor G,

Carruthers SG, Pylypchuk G, Burgess E, Lewanczuk R, Dresser GK, Penner B, Hegele RA, McFarlane PA, Sharma M, Campbell NR, Reid D, Poirier L, Tobe SW, Canadian Hypertension Education Program: The 2012 canadian hypertension education program recommendations for the management of hypertension: Blood pressure measurement, diagnosis, assessment of risk, and therapy. *Can J Cardiol* 28: 270-287, 2012

390. McArdle N, Devereux G, Heidarnejad H, Engleman HM, Mackay TW, Douglas NJ: Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 159: 1108-1114, 1999

391. Kohler M, Smith D, Tippett V, Stradling JR: Predictors of long-term compliance with continuous positive airway pressure. *Thorax* 65: 829-832, 2010

392. Weaver TE, Kribbs NB, Pack AI, Kline LR, Chugh DK, Maislin G, Smith PL, Schwartz AR, Schubert NM, Gillen KA, Dinges DF: Night-to-night variability in CPAP use over the first three months of treatment. *Sleep* 20: 278-283, 1997

393. Weaver TE, & Grunstein RR: Adherence to continuous positive airway pressure therapy: The challenge to effective treatment. *Proc Am Thorac Soc* 5: 173-178, 2008

394. Rolfe I, Olson LG, Saunders NA: Long-term acceptance of continuous positive airway pressure in obstructive sleep apnea. *Am Rev Respir Dis* 144: 1130-1133, 1991

395. Meurice JC, Dore P, Paquereau J, Neau JP, Ingrand P, Chavagnat JJ, Patte F: Predictive factors of long-term compliance with nasal continuous positive airway pressure treatment in sleep apnea syndrome. *Chest* 105: 429-433, 1994

396. Hoffstein V, Viner S, Mateika S, Conway J: Treatment of obstructive sleep apnea with nasal continuous positive airway pressure. patient compliance, perception of benefits, and side effects. *Am Rev Respir Dis* 145: 841-845, 1992

397. Krieger J, & Kurtz D: Objective measurement of compliance with nasal CPAP treatment for obstructive sleep apnoea syndrome. *Eur Respir J* 1: 436-438, 1988

398. Reeves-Hoche MK, Meck R, Zwillich CW: Nasal CPAP: An objective evaluation of patient compliance. *Am J Respir Crit Care Med* 149: 149-154, 1994

399. Ginsberg JM, Chang BS, Matarese RA, Garella S: Use of single voided urine samples to estimate quantitative proteinuria. *N Engl J Med* 309: 1543-1546, 1983